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CASE REPORT

Melanocytic Hyperpigmentation of the Tongue from Low-dose Radiotherapy

RJ Amdur,[1] PR Sandow,[2] A Yeung,[1] WM Mendenhall[1]

[1]Department of Radiation Oncology, College of Medicine, and [2]Department of Oral Medicine, College of Dentistry at the University of Florida, Gainesville Florida, USA

ABSTRACT

Several of our patients developed patches of melanotic hyperpigmentation (black spots) in the mucosa of the tongue during radiotherapy for brain tumours. The purpose of this report was to describe a representative case with a literature review. A 39-year-old African American female received 6 weeks of radiotherapy for an optic nerve meningioma. During the last week of radiotherapy, she developed patches of melanotic hyperpigmentation in the mucosa of the oral tongue that were psychologically disturbing to her. There was no associated tongue discomfort, oral inflammation, infection, or pigmentation change elsewhere. Her medical history and list of medications did not yield any potential contributing factors. The radiation dose to the oral cavity was very low (10 Gy over 6 weeks); the oral cavity received only the exit dose from a single beam angle. We elected to observe her without biopsy or treatment. After 3 months, the patches started to fade and had completely resolved 12 months following radiotherapy. We have seen several additional patients with this same feature. This is the first publication to describe patches of melanotic hyperpigmentation in the tongue from low-dose radiotherapy. Health care providers who see patients receiving radiotherapy for brain or head-and-neck tumours will benefit from our analysis of this phenomenon.

Key Words: *Hyperpigmentation; Mouth diseases; Pigmentation disorders; Radiotherapy; Tongue*

中文摘要

低劑量放射治療引致舌部黑色素沉著

RJ Amdur, PR Sandow, A Yeung, WM Mendenhall

我們曾接觸數名因腦腫瘤接受放射治療而出現舌頭黏膜黑色素沉著（黑點）的病例。本文討論其中一個具代表性的例子並回顧有關文獻。一名39歲美國黑人女性，因患上視神經鞘腦膜瘤而接受六個星期的放射治療。在放射治療的最後一個星期，病人因在舌頭黏膜上有黑色素沉著而造成心理困擾。除此以外，病人並沒有舌頭不適、口腔發炎、感染或其餘部位的色素轉變。了解病歷及病人曾服食的藥物都未能找出原因。病人口腔接受的放射劑量相當低（六個星期共10 Gy），而且口腔部分只接受單束角的出射劑量。我們決定繼續觀察，並未為病人做切片或施以其他治療。三個月後黑點開始減褪；放射治療十二個月後，黑點完全消失。我們曾接觸幾位病人有類似的情況。本文是首例有關低劑量放射治療引致舌頭黑色素沉著的病例報導，這分析報告可讓醫護人員對因腦或頭頸部腫瘤而接受放射治療的病人有更多了解。

Correspondence: *Dr RJ Amdur, 2000 SW Archer Rd, PO Box 100385, Gainesville, FL 32610-0385, USA.*
Tel: (352) 265-0287; Fax: (352) 265-7045; Email: amdurr@shands.ufl.edu

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INTRODUCTION

Patches of melanotic hyperpigmentation (black spots) in the mouth are often distressing to the patient and a management challenge for health care providers, especially when they are new or change significantly over a short time. Since oral hyperpigmentation may be a side-effect of radiotherapy, it is important for the health care team to be familiar with this possible effect and discuss it as part of the consent process with patients, before treatment begins.

Melanotic hyperpigmentation of the tongue is uncommon following radiotherapy to the mouth. We were able to find only one publication that reports tongue hyperpigmentation as a result of radiotherapy, and this was in a patient who experienced the kind of mucositis that came from a high radiation dose.[1]

Melanotic hyperpigmentation of the oral cavity has not been described purely as a consequence of low-dose radiotherapy in any setting. We use the term "low dose" to mean a dose of radiotherapy that does not cause mucositis. We have now seen several patients who developed a striking pattern of melanotic hyperpigmentation in the mucosa of the tongue during a course of radiotherapy for a brain tumour, even after very low-dose radiation to the mouth. The purpose of this report was to describe one of these cases and review the pertinent literature.

CASE REPORT

A 39-year-old African American female presented with impaired sight in one eye. A workup by a general internist, a neurologist, and an ophthalmologist revealed unilateral visual problems and a tumour of the optic nerve, consistent with meningioma. A physical examination as well as comprehensive radiological and laboratory studies were negative for autoimmune disease, multiple sclerosis, endocrinopathy, and immunodeficiency. A review of her systems was negative with the exception of decreased vision in one eye. She had a history of hypertension, and was on treatment with 10 mg of lisopril and 12.5 mg of hydrochlorothiazide daily. She took a single multivitamin daily, did not use tobacco products, and drank alcohol infrequently.

The patient was referred to our department for radiation therapy for an optic nerve meningioma. Our physical examination revealed decreased vision on the side of the tumour. On transoral examination, the oral mucosa looked healthy; there was no sign of oral infection, inflammation, or ulceration, and the teeth were in good condition. We did not take pretreatment photographs of the mouth, but there were no areas of hyperpigmentation on the tongue.

We treated her with fractionated stereotactic radiation therapy using five 6-MV photon beams with non-coplanar beam angles that intersected through the target volume. One beam was oriented so that it exited through the oral cavity. The prescription dose was 50.4 Gy at 1.8 Gy per once-daily treatment, Monday through Friday, for a total of 28 treatments over approximately 6 weeks.

During the last 2 weeks of radiotherapy (prescription dose of approximately 40 Gy), the patient complained about the appearance of her tongue. In the preceding week, she had noticed the development of black patches that were getting progressively darker and more numerous. She was concerned that these patches were a sign of a serious medical problem and that they would frighten people who were close to her when she spoke or ate. Otherwise, she was asymptomatic, with the exception of the minor taste disturbance that we expected after radiotherapy in this setting. Specifically, she denied any systemic symptoms or hypersensitivity of the tongue to pain. On physical examination there were black patches on the mucosa on the dorsum and lateral border of the tongue (Figure 1). The tongue mucosa was intact without signs of inflammation or infection. Palpation of the tongue was negative for tenderness or masses, and there was no difference in the texture of the mucosa between areas with and without hyperpigmentation. There was no hyperpigmentation or other abnormality on the ventral surface of the tongue, gingiva, palate, or buccal mucosa.

We elected to observe the tongue without biopsy or treatment. She completed radiotherapy as planned over the next 2 weeks. We saw her in follow-up 12 weeks after completing radiotherapy. She had not had any symptoms or complications from radiotherapy, systemic illness, or oral discomfort since completing the treatment and her taste had returned to normal within a few weeks. She said that the tongue hyperpigmentation had remained stable for at least 4 weeks following the completion of radiotherapy and then started to fade over about 4 weeks. On our 12-week post-treatment examination, the tongue patches were still present but had faded to about 50% of their peak intensity (Figure 1). When we examined her about 12 months later,

there was no hyperpigmentation of the tongue and no other new findings anywhere else in the mouth, as well as no history or features of any systemic disease. She explained that the tongue patches had steadily faded following our 12-week examination and were completely gone about 9 months after radiotherapy. At 5 years after completing radiotherapy, there was no hyperpigmentation in the oral cavity, her interval health history was non-contributory, and her meningioma was stable.

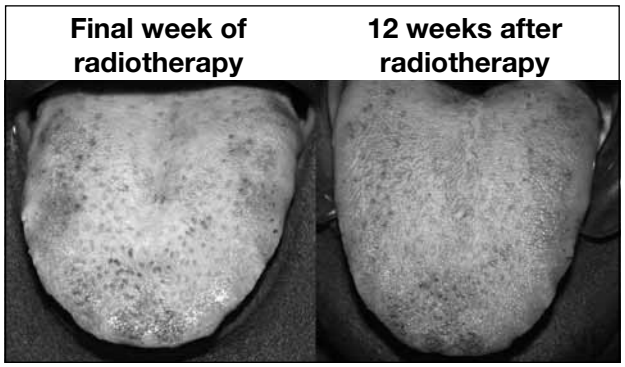

Figure 1. Patches of melanotic hyperpigmentation of the oral tongue in a patient who received radiotherapy for an optic nerve meningioma. The oral cavity received only the exit dose from a single beam angle. Hyperpigmented patches developed during the last 2 weeks of a 6-week course of radiotherapy, were stable for about 4 weeks following the completion of treatment, and faded by about 50% by 12 weeks post-radiotherapy. The patient reported that the patches were completely gone 9 months after radiotherapy.

DISCUSSION

Over the past 5 years we have managed 3 patients with the type of tongue hyperpigmentation described in this case report. The main details of these cases were identical — African American ethnicity; radiotherapy for a brain tumour with a beam exiting through the oral cavity. Moreover, there was no relevant medical history, and she had no current conditions nor was she taking medications known to cause oral hyperpigmentation. These hyperpigmented patches were limited to the oral tongue, developed near the end of a 5- to 6-week course of radiotherapy without signs of oral inflammation or infection, persisted for about 3 months, and then gradual faded. There was complete resolution within 12 months of completing radiotherapy.

In each of our patients with tongue hyperpigmentation, there was distress about the appearance of their tongues

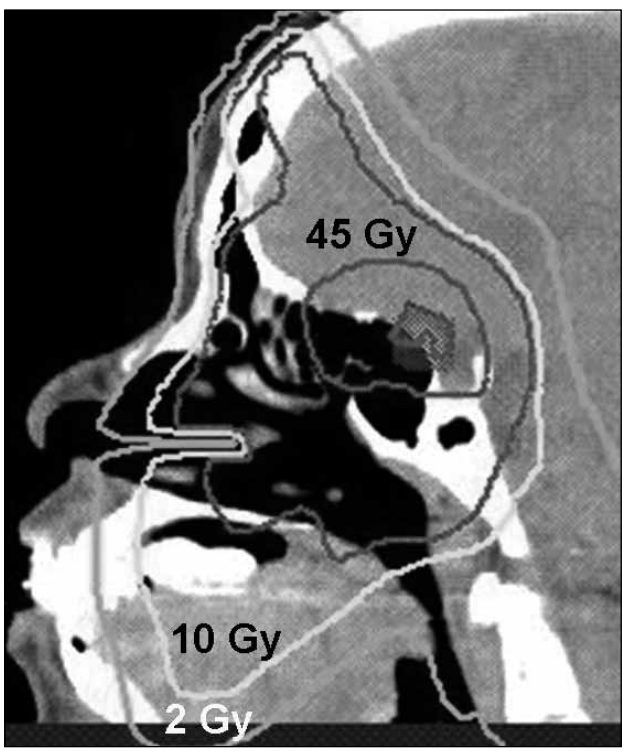

Figure 2. Radiation dosimetry of the patient in Figure 1 who developed patches of hyperpigmentation on the tongue during radiotherapy. The dose to the oral cavity was very low—approximately 10 Gy at 0.36 Gy per treatment—with treatment delivered over 6 weeks.

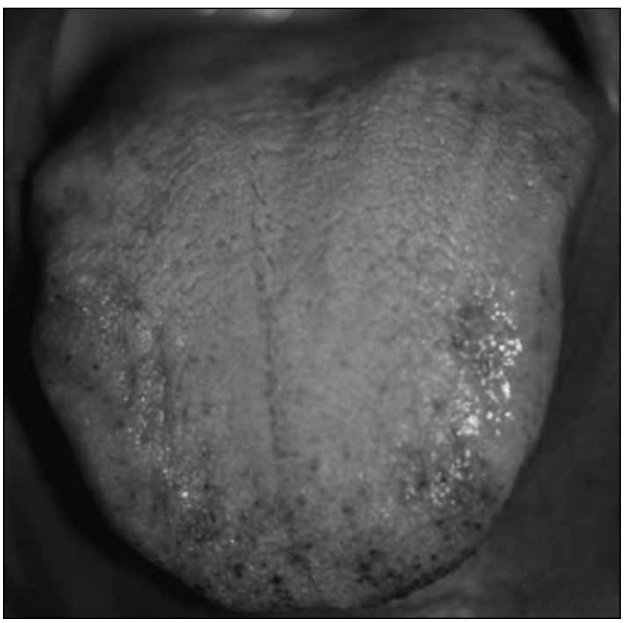

Figure 3. Dark brown pigmentation of the dorsum of the tongue after initiation of peginterferon alfa and ribavirin combination therapy for hepatitis C. (De Moraes PC, Noce CW and colleagues. Tongue hyperpigmentation resulting from peginterferon alfa and ribavirin combination therapy. A case report. JADA 2009;140(11);1377-9. Copyright © 2009 American Dental Association. All rights reserved. Reproduced by permission.)

and most health care providers involved in the caring for these patients did not know how to advise them regarding additional diagnostic studies or treatment.

This pattern of tongue hyperpigmentation was an unusual reaction to low-dose radiation exposure. To evaluate the radiation dose to the oral cavity, we reconstructed the radiation dose distribution in patients who developed tongue hyperpigmentation. Figure 2 shows the dosimetry from the case presented in this paper. In all 3 patients, the dose to the oral cavity was similar (approximately 10 Gy at 0.35 to 0.40 Gy per treatment over 5 to 6 weeks). Doses in this range are well below the level at which we encounter mucositis, or any degree of inflammation due to radiation damage to the oral mucosa.

Literature Review

Ours is the first report of melanocytic hyperpigmentation of the oral cavity purely from low-dose radiotherapy. The only publication that describes oral hyperpigmentation as a direct result of radiotherapy was the 1994 paper by Barrett et al[1] that we summarised in the Introduction. The major difference between their findings and ours is that they reported hyperpigmentation following radiation-induced necrosis of the oral epithelium.

There are many review articles and book chapters that discuss the differential diagnosis and management of pigmented lesions of the oral mucosa.[2] A comprehensive discussion of this subject is beyond the scope of this paper. Suffice it to say that radiation therapy is not listed as a causative factor in the articles we reviewed. Similarly, oral hyperpigmentation is not mentioned in review articles that focus on the oral sequelae of radiotherapy.[3]

There are multiple publications that describe hyperpigmentation of the tongue from the medications that are most commonly used to treat hepatitis C infections — pegylated interferon and ribavirin.[4] de Moraes et al[5] have reported a pattern of tongue hyperpigmentation that appears to be identical to what we observed in our radiotherapy patients (Figure 3).[5] In some publications, the authors explain that the main responsible risk factor was a dark skin[4] and the mechanism of hyperpigmentation was thought to be upregulation of alpha melanocyte–stimulating hormone receptors by the interferon.[6]

There is no study that documents the mechanism of oral hyperpigmentation from radiotherapy and we are not prepared to speculate on this. Whatever the mechanism, it must be transient because the hyperpigmentation resolved within 12 months. Interestingly in our patients, hyperpigmentation occurred only on the tongue, and not on the palate, buccal mucosa or gingiva. We do not have an explanation for this omission, as hyperpigmentation of these areas (that do contain melanocytes) does occur in other settings.

CONCLUSIONS

Hyperpigmentation of the tongue is a potential consequence of low-dose irradiation (i.e. a dose that does not cause mucosal discomfort or inflammation) of the oral cavity. It is important for health care providers to recognise this pattern of tongue hyperpigmentation as a temporary reaction that does not require biopsy or treatment. We recommend informing African American patients who are to receive an exit dose to the oral cavity (as often occurs during radiotherapy for a brain tumour) about the possibility of tongue hyperpigmentation so that they are not alarmed if it develops.

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