

Tongue Hyperpigmentation Associated with Temozolomide as a Single Agent: Case Report

Hiperpigmentação da Língua Associada a Temozolomida em Monoterapia: Caso Clínico



Lúcia GIL¹, Joana MARQUES², Duarte SALGADO²
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ABSTRACT

Hyperpigmentation of the tongue has been associated with chemotherapy, specifically cytotoxic drugs, but the exact pathophysiological mechanism is still not well understood. We describe a 37-year-old black woman that presented with tongue hyperpigmentation one week after the initiation of chemotherapy with temozolomide as a single agent. No cases of tongue hyperpigmentation associated with temozolomide as a single agent have been reported before. The diagnosis of drug associated pigmentary changes is based on the confirmation the onset of the clinical observations shortly after the initiation of the chemotherapy agent. The tongue hyperpigmentation is usually self-limited. This case constitutes a challenge for healthcare professionals and patients and emphasizes the importance of documenting these cases in order to guide healthcare professionals in managing the expectations of the patients and the potential adverse effects associated with certain drugs.

Keywords: Hyperpigmentation/chemically induced; Temozolomide/adverse effects; Tongue Diseases/chemically induced

RESUMO

A hiperpigmentação da língua tem sido associada a quimioterapia, especificamente a fármacos citotóxicos, mas o mecanismo fisiopatológico exato não é conhecido. Apresentamos o caso clínico de uma mulher de raça negra, de 37 anos que apresentou hiperpigmentação da língua uma semana após o início da quimioterapia com temozolomida em monoterapia. Nenhum caso de hiperpigmentação da língua associada à temozolomida em monoterapia foi antes relatado. O diagnóstico de alterações pigmentares associadas ao medicamento é baseado na correlação temporal do início dos achados clínicos com o início do agente quimioterápico. A hiperpigmentação da língua geralmente é autolimitada. Este caso constitui um desafio para os profissionais de saúde e para os doentes e enfatiza a importância de documentar estes casos, a fim de orientar os profissionais de saúde na gestão das expectativas dos doentes e dos potenciais efeitos adversos associados a determinados fármacos.

Palavras-chave: Doenças da Língua/induzida quimicamente; Hiperpigmentação/induzida quimicamente; Temozolomida/efeitos adversos

INTRODUCTION

Drug-induced pigmentation accounts for up to 20% of all cases of acquired pigmentation.¹ Hyperpigmentation of the tongue has been associated with chemotherapy, specifically cytotoxic drugs, but the exact pathophysiological mechanism is still not well understood.¹ Temozolomide appears in the literature associated with tongue hyperpigmentation in combination therapy.² No cases of tongue hyperpigmentation associated with temozolomide as a single agent have been reported before. We describe a woman of African ancestry who was receiving chemotherapy with temozolomide as a single agent and developed tongue hyperpigmentation.

CASE REPORT

A 37-year-old black woman was diagnosed with Isocitrate dehydrogenase (IDH) wild-type glioblastoma in the left parietal lobe, in another hospital center, in August 2020. She was treated initially with left parietal craniotomy with excision of lesion. The surgery was followed by focal radiation therapy (RT) and a course of concomitant daily temozolomide at 75 mg/m² in September 2020, at our hospital. The patient was previously treated with levetiracetam and

during chemotherapy, she was treated with ondansetron according to the protocol. One week after the initiation of chemotherapy with daily temozolomide as a single agent, the patient presented multiple black macules on the dorsal surface of the tongue, without any associated symptoms (Fig. 1). She never had similar lesions in the past, nor change in the color of the palms, fingernails or other parts of the body. At the same time, the radiotherapy and concomitant chemotherapy with temozolomide (Stupp protocol) was interrupted, following the histological revision of the tumor at our hospital to a diagnosis of embryonal tumor (World Health Organization - WHO, Grade IV). The patient started neuro-axis RT with boost to the residual lesion plus Vincristine weekly, according to the Packer protocol. Two months after stopping temozolomide chemotherapy, there was an improvement in patient's tongue hyperpigmentation with almost complete resolution (Fig. 2).

DISCUSSION

Temozolomide is an alkylating agent that performs the alkylation of adenine/guanine residues, leading to DNA damage, thus inhibiting DNA and cellular replication.

1. Department of Oncology. Setubal Hospital Center. Setubal. Portugal.

2. Department of Neurology. Portuguese Institute of Oncology Francisco Gentil. Lisbon. Portugal.

✉ **Autor correspondente:** Lúcia Gil. luciamgil@hotmail.com

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Figure 1 – Frontal view of the tongue with multiple macular areas of hyperpigmentation, one week after chemotherapy with temozolomide as single agent



Figure 2 – Frontal view of the tongue, two months after stopping chemotherapy with temozolomide as single agent

It is indicated in the treatment of glioblastoma multiforme, anaplastic astrocytoma, Ewing's sarcoma, neuroendocrine tumors, pituitary tumours and other tumors.³

Antineoplastic therapy, as a single agent or combination drug, can be associated with several side effects including dermatological, neurological, gastrointestinal and others.² Hyperpigmentation of the tongue has been associated with various chemotherapy agents, specifically cytotoxic drugs, that commonly induce pigmentation and may affect the hair, nails, and mucous membranes in local or diffuse patterns.^{1,2,4,5} Although the exact pathophysiological mechanism is still not well understood, four mechanisms of drug-induced pigmentation are suggested. The first mechanism may be associated with stimulation of the excessive production of melanin and deposition on the lingual mucous membrane; the second mechanism involves accumulation of the drug, saturating dermal macrophages, which are unable to eliminate these foreign bodies; the third mechanism involves synthesis of new pigment, such as lipofuscin, under the direct influence of the insulting drug. The fourth mechanism involves deposition of iron: drug-induced dermal vascular damage may induce leakage of red blood cells into the dermis, and subsequent lysis of these red blood cells throughout the dermis can result in pigmentation.¹ Hyperpigmentation of the tongue following a treatment with chemotherapy has been reported with several single agents such as doxorubicin, cyclophosphamide, capecitabine and Adriamycin.^{4,6-9} A report of tongue hyperpigmentation and brown longitudinal streaking with blue lunular pigmentation of the fingernails and toenails has been described following use of combination chemotherapy involving cisplatin, ifosfamide, temozolomide, and vincristine.² Drug-induced

pigmentation often occurs slowly and worsens over the course of months to years upon initiation of the offending agent.² The tongue hyperpigmentation, previously described, is usually self-limited and disappears a few weeks after treatment is completed.⁴ There are not reported cases of tongue hyperpigmentation associated with levetiracetam and ondansetron.

This case constitutes a challenge for healthcare professionals and the patient, as it is not an expected or described side effect in temozolomide monotherapy, which emphasizes the importance of documenting these cases in order to guide healthcare professionals in managing the expectations of the patients and also the potential adverse effects associated with certain drugs.

AUTHORS CONTRIBUTION

LG: Draft of the manuscript, literature research, corresponding author.

JM, DS: Contributed to the draft of the manuscript, critical review, approval of the final version.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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