# Mucocutaneous Hyperpigmentation Associated with Hydroxyurea Therapy in a Patient with Essential Thrombocythemia: Case Report

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*Hiperpigmentação Mucocutânea Associada à Terapia de Hidroxiureia em Paciente com Trombocitemia Essencial: Relato de Caso*

Hiperpigmentación Mucocutánea Asociada al Tratamiento con Hidroxiurea en un Paciente con Trombocitemia Esencial: Informe de Caso

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***ABSTRACT***

**Introduction:** Mucocutaneous hyperpigmentation is a dermatological condition that may be related to chemotherapy treatments, such as therapies using hydroxyurea (HU). HU is a cytostatic drug widely used in myeloproliferative diseases and is the main line of treatment for essential thrombocythemia (ET). The present study aims to report a rare case of mucocutaneous hyperpigmentation in a patient with ET. **Case report:** Male patient, 68 years old, 89 kg, diagnosed with ET using HU 2 g/day. After three months of therapy, he presented hyperpigmented brownish-colored lesions on the hands and oral cavity (tongue). In a decision shared with the assistant physician, the patient chose to continue using the drug. After six years of follow-up, the lesions remain stable. **Conclusion:** Mucocutaneous hyperpigmentation associated with HU therapy is a benign event secondary to the use of the drug and does not require discontinuation of use, however, its withdrawal or dose reduction usually leads to the reduction or disappearance of the lesions.

**Key words:** hyperpigmentation; hydroxyurea; thrombocythemia, essential.

RESUMO

**Introdução:** A hiperpigmentação mucocutânea é uma condição dermatológica que pode estar relacionada a tratamentos quimioterápicos, a exemplo das terapias com uso de hidroxiureia (HU). A HU é um fármaco citostático de amplo uso nas doenças mieloproliferativas e compõe a principal linha de tratamento da trombocitemia essencial (TE). O presente estudo tem por objetivo relatar um caso raro de hiperpigmentação mucocutânea em um paciente com TE. **Relato do caso:** Paciente do sexo masculino, 68 anos de idade, 89 kg, com diagnóstico de TE, em uso de HU 2 g/dia. Com três meses de terapia, apresentou lesões hiperpigmentadas de coloração acastanhadas em pele das mãos e mucosa oral (língua). Em decisão partilhada com o médico-assistente, o paciente optou pela continuação do uso do medicamento. Após seis anos de acompanhamento, as lesões mantêm-se estáveis. **Conclusão:** A hiperpigmentação mucocutânea associada à terapia com HU é um evento benigno secundário ao uso do fármaco e não exige a interrupção de uso, porém, sua retirada, ou redução das doses, geralmente leva à diminuição ou ao desaparecimento das lesões.

**Palavras-chave:** hiperpigmentação; hidroxiureia; trombocitemia essencial.

RESUMEN

**Introducción:** La hiperpigmentación mucocutánea es una condición dermatológica que puede estar relacionada con tratamientos de quimioterapia, como las terapias con hidroxiurea (HU). La HU es un fármaco citostático ampliamente utilizado en enfermedades mieloproliferativas y es la principal línea de tratamiento de la trombocitemia esencial (TE). El presente estudio tiene como objetivo reportar un caso raro de hiperpigmentación mucocutánea en un paciente con TE. **Informe del caso:** Paciente masculino de 68 años, 89 kg, diagnosticado de TE mediante HU 2 g/día. A los tres meses de tratamiento presenta lesiones hiperpigmentadas de color pardusco en manos y cavidad oral (lengua). En una decisión compartida con el médico asistente, el paciente optó por continuar usando el medicamento. Tras seis años de seguimiento, las lesiones se mantienen estables. **Conclusión:** La hiperpigmentación mucocutánea asociada a la terapia con HU es un evento benigno secundario al uso del fármaco y no requiere la suspensión de su uso, sin embargo, su retirada o reducción de dosis suele conducir a la reducción o desaparición de las lesiones.

**Palabras clave:** hiperpigmentación; hidroxiurea; trombocitemia esencial.

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## INTRODUCTION

Hydroxyurea (HU) is a cytostatic medication which acts by inhibiting the enzyme ribonucleotide reductases in the phase S of cellular replication blocking the DNA synthesis and cellular division[1-3]. HU is frequently utilized in myeloproliferative diseases as a reversible myelosuppression agent effective in reducing platelets count with low level of hepatorenal toxicity and few drug interactions[1,3-8].

HU adverse effects are dose-dependent and reversible in up to 43% of the cases[7,9,10]. Tissues with high rate of cellular renovation as skin, mucosa and nails are target-sites of the drug[11]. Table 1 describes HU[2,3,6,7,9,10] related dermatological adverse effects.

**Table 1**. Dermatologic and stomatological manifestations secondary to hydroxyurea use

| Manifestations of lower complexity | Manifestations of higher complexity |
|---|---|
| Mucocutaneous hyperpigmentation | Leg ulcers |
| Skin xerosis | Actinic keratosis |
| Skin ulcerations | Skin carcinoma |
| Lichenoid skin rashes | |
| Alopecia | |
| Oral aphthosis | |
| Dermatomyositis-like erythema | |
| Chromonychia | |
| Skin atrophy | |
| Desquamation of the face, hands and feet ' | |

Notification of HU-related cutaneous toxicity is underestimated since the clinic is not exuberant and the course is benign[7,10]. Melanonychia is reported for most of the cases and hyperpigmentation of the oral cavity involving or not the tongue is rare[1,3,7,12].

Essential thrombocythemia (ET) is a clonal chronic myeloproliferative disease with platelets count greater or equal to 450,000/μL in two distinct occasions: presence of at least one mutation of the genes *Janus kinase 2* (JAK2), *calreticulin* (CALR) and/or *muscle lim protein* (MPL) and exclusion of other thrombocytosis determinant etiologies[4,13]. Bone marrow evaluation is essential for differential diagnosis[4]. ET manifests with erythromelalgia, thrombotic phenomena, mainly arterial, hemorrhages and risk of spontaneous miscarriage[4,14].

It is suggested acid acetylsalicylic to treat ET to prevent thrombosis in older adults and patients with no high risk of thrombosis. Otherwise, the first line of treatment is HU followed by pegylated alphainterferon[4]. Patients with platelets lower than 150.000/μL should not submit to cytoreductive therapy[14]. Even if unable to change the history, not preventing fibrotic or leukemic progression, HU is prescribed to prevent thrombotic complications, mainly in individuals with mutation JAK2[4,14].

The authors report a type of secondary mucocutaneous hyperpigmentation to the use of HU in patient with ET and compared with other reports of hyperpigmentation of oral mucosa with involvement or not of the tongue associated with HU and discuss the respective literature. The databases PubMed and SciELO were references for a short literature review in Portuguese and in English with the descriptors "hyperpigmentation" and " hydroxyurea", involving original review articles and case reports published between 1974 and July 2022. The Institutional Review Board of "*Centro Universitário Presidente Antônio Carlos (Unipac-JF)*" approved the study, report 5,515,386 (CAAE (submission for ethical review): 59254322.0.0000.5156).

## CASE REPORT

Man, 68 years of age, 89 kg, Brown race, presented splenomegaly in March 2016, the ultrasound revealed the spleen measuring 14.5 cm in its longest diameter and was referred to the Hematology. Three proliferative-related diseases lab tests with 60 days interval showed persistent thrombocytosis (549,000/μL, 650,000/μL, 1,000.000/μL), elevation of the levels of lactic dehydrogenases (549 UI/L, 690 UI/L and 720 UI/L) and beta2-microglobuline (3.1 g/mL, 3.7 g/mL and 3.8 g/mL).

The patient was submitted to bone marrow biopsy revealing megakaryocytic hyperplasia. The study of mutation of JAK2 was positive with normal medullar karyotype and negative BCR-ABL. The diagnosis of ET was confirmed, and the patient, after briefed about HU adverse effects described in the Informed Consent Form (ICF) initiated the treatment. Three months later, the patient presented brownish lesions at the labial mucosa, back of the tongue and hands (Figure 1).

The patient had already been informed about HU-related adverse events and decided to continue with the drug. He is being monitored for six years with month consultations with hematologist and annually with the dermatologist and in use of HU 2 g/day, in good clinical conditions, correction of platelet count and mucocutaneous hyperpigmentation keeping the same initial aspect.

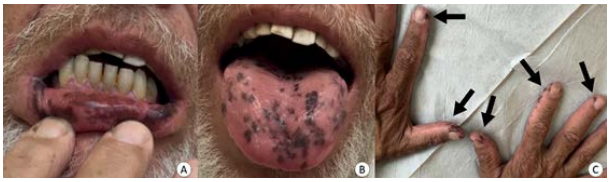

**Figure 1**. A) Hyperpigmentation of labial mucosa; B) Hyperpigmentation of the surface of the back of the tongue; C) Hands with hyperchromic spots at the back and palm region without associated ungual involvement (black arrows)

## DISCUSSION

To the best of the authors knowledge, this is the global 12th report on oral hyperpigmentation associated with HU therapy. Table 2[1,3,8,12,15-21] compares reports of compromise of oral mucosa involving or not the tongue.

HU-induced non-ulcerative cutaneous toxicity occurs in 1.6% of the patients only[22]. However, 96% of the patients with myeloproliferative diseases can have HU-provoked cutaneous lesions and induced hyperpigmentation can reach 50%[8,23]. Of the 12 reports of mucocutaneous hyperpigmentation in the oral cavity with involvement of the tongue or not, ten presented baseline myeloproliferative diseases[1,3,12,15,16,18-21].

No established relation between the dose of HU, time of use and appearance of hyperpigmentation exists[1,3] and in addition, cutaneous lesions have no predictable distribution[3,7,10]. Dermatologic side effects are more prevalent in long-term treatments and it is believed there is genetic predisposition associated with it[3,9-11,22]. The mean time of onset of hyperpigmentation of the 12 cases portrayed in Table 2[1,3,8,12,15-21] was one year and six months, mode of three months and the mean age of 11 cases was 54.6 years with modes of 61 and 68, with slight prevalence of males. The mean dose of HU was not determined because of the daily variation or lack of this information in some cases reported[1,3,8,12,15-21].

Dermatologist follow-up is mandatory for long-term drug intake[2,11] and also due to the possibility of malignant actinic keratosis transformation, understood as a HU-

**Table 2**. Case reports of hyperpigmentation of oral mucosa and/or tongue by hydroxyurea

| Author | Year | Age of the patient | Sex | Disease treated | Time of use of hydroxyurea* | Dose | Location |
|---|---|---|---|---|---|---|---|
| Majumdar et al.[15] | 1990 | 61 years | Male | Chronic granulocytic leukemia | 4 years | 9 g/day | Oral mucosa, hands and forehead |
| Gropper et al.[16] | 1993 | 63 years | Female | Polycythemia vera | 8 months | 500 mg-1.5 g/day | Labial mucosa, toes and feet nails |
| Laughon et al.[17] | 2000 | 51 years | Female | Human immunodeficiency virus | 1 month | Not reported | Tongue, labial mucosa, perioral region, palms and soles, nails of feet and hands |
| Kumar et al.[8] | 2002 | Adult | Male | Psoriasis | 9 weeks | 1-1.5 g/day | Tongue, skin and nails |
| Issaivanan et al.[18] | 2004 | 10 years | Male | Chronic myeloid leukemia | 3 months | 40 mg/kg/day | Hands, feet, face, neck, tongue, nails of the hands and feet |
| Nofal e El-Din[19] | 2012 | 68 years | Female | Chronic myeloid leukemia | 9 years | 1-1.5 g/day | Tongue and nails |
| Murray et al.[20] | 2016 | 63 years | Male | Essential thrombocythemia | 2 years (nails), 4 years and 5 months (tongue) | Not reported | Tongue, skin and nails |
| Algarra et al.[21] | 2017 | 45 years | Male | Essential thrombocythemia | 1 year | Not reported | Tongue, skin and nails |
| Neculisean et al.[1] | 2019 | 61 years | Male | Essential thrombocythemia | 3 months | 1.5 g/day | Tongue, skin and nails |
| Veillet-Lemay e Haber[3] | 2018 | 44 years | Female | Essential thrombocythemia | 3 months | 1 g/day | Tongue and nails |
| Alshammasi et al.[12] | 2020 | 67 years | Female | Polycythemia vera | 1 year and 5 months | 500 mg/day | Bilateral oral mucosa, gingiva, back of the tongue, hard palate, skin and nails |
| Current clinical report | 2022 | 68 years | Male | Essential thrombocythemia | 3 months | 2 g/day | Surface of the back of the tongue, labial mucosa and hands |

(*) To treat hyperpigmentation.

related possible manifestation of major complexity[2,11]. The patient investigated is followed-up annually by the dermatologist.

Mucocutaneous hyperpigmentation secondary to HU does not require discontinuation of the treatment; the withdrawal or reduction of the doses can diminish or determine the disappearance of the lesions[7,10,11]. Upon agreement with the hematologist and the patient in face of the specificities of the case, the dose of HU was kept with no progression or regression of the lesions.

## CONCLUSION

The clarification to the patients before the therapy about the possible adverse effects of HU can minimize or mitigate the anxiety in face of its potential onset. Mucocutaneous hyperpigmentation associated with HU is benign, dose-unrelated and does not require discontinuation of the drug. Tongue is the most common site when this rare occurrence affects the oral cavity and the most compromised patients are those diagnosed with ET.

### CONTRIBUTIONS

Daniela de Oliveira Werneck Rodrigues, Augusto Cézar Apolinário dos Santos, Nathália Chebli de Abreu and Monica Albuquerque Costa contributed to the study design, acquisition, analysis and interpretation of the data, wording and critical review. Thais Sette Espósito, Lucas Augusto Niess Soares Fonseca, Lucas Barra Mathiasi; Nathalia Noyma Sampaio Magalhães and Júlia Campos Fabri contributed to the study design, acquisition, analysis and interpretation of the data. All the authors approved the final version to be published.

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### DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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