

# Acquired Hyperpigmentation of the Tongue Associated with Hydroxyurea: Case Report of a Very Rare Location of a Rare Adverse Effect

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**Abstract:** Changes in pigmentation has been reported for differing chemotherapeutic agents, such as cyclophosphamide, anthracyclines as well as hydroxyurea. Generalized hyperpigmentation as well as melanonychia has been well reported for hydroxyurea, which is neither dose dependent or related to the duration of treatment. It has never been report a case of hyperpigmentation of the tongue associated with the use of hydroxyurea, although it has been reported with other chemotherapeutic agents. We report a case of hyperpigmentation of the tongue associated with the use of hydroxyurea, discuss the differential diagnosis and a review the literature.

**Keywords:** Hydroxyurea, hyperpigmentation, chemotherapeutic, tongue, melanosis.

## INTRODUCTION

Hydroxyurea is an antineoplastic agent used to treat myeloproliferative disorders such as essential thrombocytosis, polycythemia rubric vera and chronic myeloid leukemia. Its mode of action is through the inhibition of DNA synthesis. Cases of hydroxyurea induced hyperpigmentation of the skin and melanonychia have been reported [1-3], however pigmentation of the tongue is a very rare event.

## CASE REPORT

A 63 year old otherwise healthy man diagnosed with essential thrombocythemia 5 years ago. He had never smoked, is from hispanic in origin and is not taking any other medication. He has been treated with hydroxyurea for the same period of time. Two years after starting hydroxyurea he noticed that his skin was darkening and that there was progressive darkening of all the nails in the form of longitudinal bands. The hyperpigmentation and longitudinal melanonychia was attributed to hydroxyurea therapy. After four and half years of therapy he noticed that three brown-pigmented

lesions had appeared on the tongue without causing him any symptoms.

Physical examination revealed three brown irregular macular-pigmented lesions with well-defined borders of between 8-10 mm in size and uniform in color (Figure 1). There was no difference in the appearance of the tongue surface between the pigmented areas and non-pigmented areas. There were no other pigmented lesions in the oral cavity or lips. A biopsy was performed to rule out mucous malignancy, which showed minimal parakeratosis with melanin pigment and macrophage accumulation in the sub epithelial connective tissue.

Also serum TSH, fasting serum cortisol and ferritin levels were solicited, resulting normal, ruling out common systemic causes implicated in hyperpigmentation.

## DISCUSSION

Hydroxyurea is a cytostatic agent that inhibits DNA synthesis and promotes cell death in the S phase of the cell cycle [4]. It is thought to cause hyperpigmentation by activating the melanocytes and increasing the production of melanin without increasing cell number

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**Figure 1:** Hypermelanosis of the tongue well demarcated.

[5]. Although decreasing the dose of hydroxyurea or discontinuing therapy with hydroxyurea could decrease or eliminate the hyperpigmentation, the chronic nature of the underlying myeloproliferative disorder and the few alternative treatments make a therapeutic change very difficult. This adverse effect is not life threatening and is not considered sufficient to stop hydroxyurea treatment in patients with essential thrombocytosis, according to a unified definition of clinical resistance or intolerance to the drug; however it may precede more serious complications such as ulceration or cancer development [6].

Unlike other chemotherapeutic agents such as doxorubicin and cyclophosphamide which have been implicated in hyperpigmentation of the tongue [7], the effect caused by these drugs appears within a few weeks of started the therapy and disappears within a few months of finishing it. In comparison the effect of hydroxyurea may take years to develop and is not considered to be dose dependent or time related [3].

Other drugs that have been implicated in lingual hyperpigmentation include alfa-interferon, ribavirin [8], minocycline [9], and imatinib [10, 11].

## CONCLUSION

Although hydroxyurea should be added to the differential diagnosis of lingual hyperpigmentation, the transformation of benign lingual pigmentation into melanoma or pigmented squamous cell cancer should be considered. Therefore careful correlation of the

clinical appearance and biopsy histology is necessary to arrive at the appropriate diagnosis and prognosis of oral pigmented lesions.

## CONFLICT OF INTERESTS

The authors report no conflicts of interest.

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