

Original Research Article

Oral Squamous Cell Carcinoma Associated with Hydroxyurea Therapy

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Abstract: We present the unique case of a patient with polycythemia Vera who developed oral cancer after 10 years of hydroxyurea therapy. Oral lesions are rare complications of long-term hydroxyurea treatment and may be an indication of stopping therapy. He died not from his malignancies, but from a splenectomy after splenomegaly disorder.

Keywords: polycythemia, malignancies, splenectomy

INTRODUCTION

Hydroxyurea (HU) is an antimetabolic agent used for treatment of myeloproliferative disorders, hematological diseases including chronic myelogenous leukaemia, polycythemia vera and essential thrombocythemia, severe psoriasis and to inhibit viral replication in HIV disease [1-3].

Long-term HU therapy has been associated with mucocutaneous changes such as (xerosis, ichthyosiform lesions, dark brown pigmentation of skin folds and nails, malleolar ulcers, oral mucositis and ulcers) and/or carcinomas [1]. Dermatological side effects are frequently seen in patients receiving long term HU therapy. Cutaneous ulcers have been reported occasionally [4]. Cutaneous side effects, hyperpigmentation, scaling, erythema and desquamation of the face and hands, skin atrophy, nail changes, and partial alopecia [4].

In C. Vassallo *et al.*; study, twenty-one out of 158 patients (13%) with chronic myeloid leukaemia treated with hydroxyurea were affected by severe and heterogeneous cutaneous and mucosal changes [5]. The association between HU and multiple aggressive squamous cell carcinomas, Bowen's disease, and multiple actinic keratoses in photo exposed areas after a variable latency period has been increasingly reported in the literature [6].

Since the first report in 1992, there have been an increasing number of case reports of SCC developing in association with hydroxyurea use. Some of these cases have died from metastatic SCC [6]. G. E. PAMUK *et al.*; present the case of an elderly male patient with chronic myeloid leukaemia (CML) in chronic phase who developed squamous cell carcinoma (SCC) metastatic to the parotid gland and regional lymph nodes after years of continuous therapy with hydroxyurea [7].

CASE REPORT

A 57-year-old man came to the department of oral medicine, Hamadan University of Medical Sciences, for investigation of maxillary and mandibular alveolar ridge to replacement his complete dentures. His chief complaint was mild pain and burning sensation and discomfort during mastication for 2 months. The patient was nonsmoker and he had no history of tobacco and alcohol.

In the patient's medical history, he had been affected by polycythemia Vera for 10 years which were under control. He was treated by Hydroxyurea within 10 years. Extra orally, there was no cervical lymphadenopathy. Intraoral examination revealed a white and red plaque like lesion under the mandibular denture on the midline area of alveolar ridge with measuring 2 cm at mesiodistal dimension that extending from the right lateral incisor region to the left lateral incisor region. The lesion was involving the top of

alveolar ridge and extends to mucogingival line in labial and lingual aspect.

Size of the lesion was not changed more and there was no bleeding. No history of similar or any oral lesion was reported in past dental history. The panoramic and periapical radiograph revealed no bony changes in the region. The differential diagnosis was plaque like candidiasis, leukoplakia, frictional keratosis due to dentures unfitness and OSCC. The patient was advised to discontinue the use of the dental prosthesis for 2 week .After 2 weeks the lesion did not recede. Under local anesthesia incisional biopsy was performed and the specimen was submitted for histopathological examination, which revealed a malignant neoplastic

proliferation of stratified squamous epithelial cells. The lesional cells by eosinophilic cytoplasm with large, often darkly staining (hyperchromatic) nuclei and an increased nuclear-to-cytoplasmic ratio with pleomorphism by produce of sheets and islands of cells proliferate within the connective tissue. In some areas an individual cell keratinization and keratin pearls formation was observable.

The histopathological diagnosis was squamous cell carcinoma and the patient was referred to oral and maxillofacial department to management the lesion. He was hospitalized for splenomegaly that accrued concomitantly with oral lesion. Unfortunately he was dead after splenectomy.

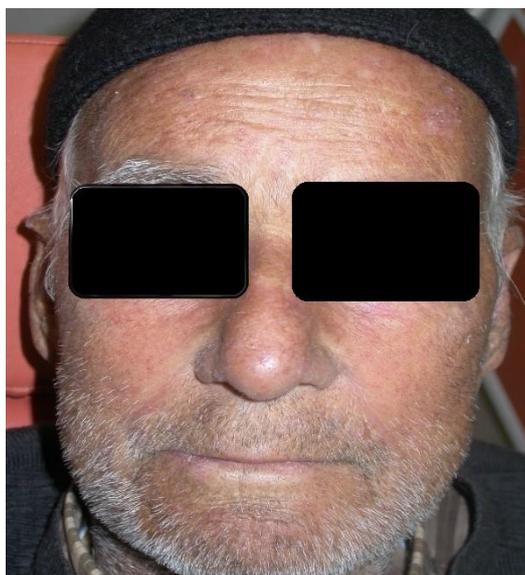


Fig 1: Extra Oral View



Fig 2: Lip desquamation associated with long-term hydroxyurea treatment



Fig 3: Clinical aspect of the carcinoma of the anterior mandibular alveolar ridge presenting as a non-bleeding ulcer

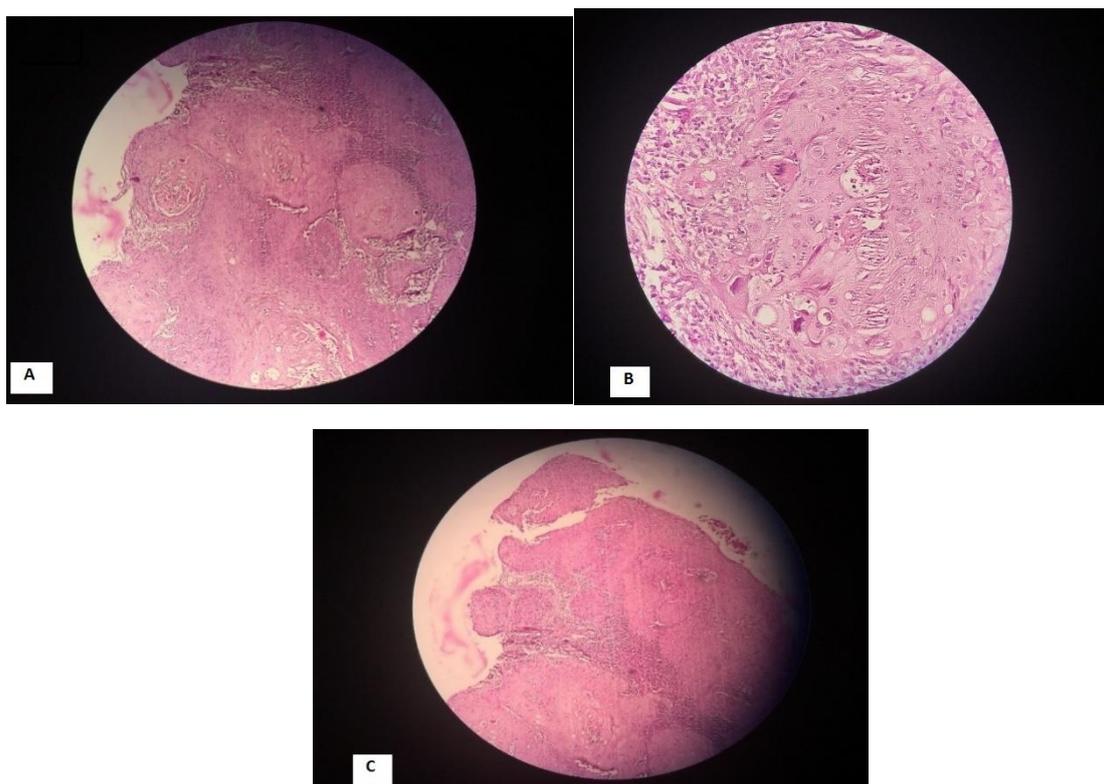


Fig 4: Histopathologic features. Infiltrating squamous cell carcinoma. Magnification 40 X, (H&E staining)

DISCUSSION

This is an unusual case of oral SCC in a 57-year-old male patient with a white and red plaque like lesion occurred following long-term hydroxyurea therapy.

Side effects of hydroxyurea therapy and relation between this agent and skin and oral cancer are documented and have been reported before. Hydroxyurea is a well-tolerated agent [8]. The effect of hydroxyurea on skin and oral mucosa usually occur following long-term therapy. Muco-cutaneous adverse effects in patients who are treated with hydroxyurea are xerosis, ichthyosis lesions, skin and nails pigmentation and malignant tumors. Oral lesions are much rarer and often present as painful ulcers associated with skin lesions. Oral mucositis and oral ulcers, glossitis,

stomatitis, fissuring and flattening of mucosal papillae may be observed [2]. Cutaneous side effects of the drug are include leg ulcers, fixed drug eruption, diffuse hyperpigmentation, brown nail discoloration, photosensitization, oral ulceration, stomatitis, and cutaneous vasculitis [8]. Development of oral malignant tumors as a complication of hydroxyurea treatment is rare [1]. The incidence of developing squamous cell carcinoma in sun-exposed areas in patients treated with long-term hydroxyurea therapy, enhanced [5]. An increased frequency of SCC has been reported in association with hydroxyurea [7]. Squamous cell carcinomas have been associated with hydroxyurea treatment [9]. Complete remission of adverse effects is usually observed after withdrawal of the medication [1-5]. Healing of the oral lesions is much faster than cutaneous lesions [2]. At the beginning of therapy with

hydroxyurea, Patients should undergo a dermatological examination [7]. It should be pointed that as hydroxyurea also provokes oral ulcers and mucositis, there could be a delay in early detection of oral SCC and clinicians must be well aware of this [1]. Hydroxyurea is a potent inhibitor of DNA synthesis and induce chromosome damage and inhibition of DNA repair in human cells [10].

CONCLUSIONS

Patients especially those with myeloproliferative disorders that undergoing hydroxyurea should have routine dermatology follow-up prior and during the therapy, since early recognition of alterations allows the reduction of comorbidities related to disease or therapy. Presence of oral lesions may be an indication for dose reduction, discontinuation or replacement of therapy [2, 6].

After suspension of hydroxyurea, the cutaneous side-effects in patients with myeloproliferative disorders disappear or improve. This confirms the crucial role of hydroxyurea in inducing this muco-cutaneous complex of lesions and demonstrates the minor role of the hematological disease itself in inducing these changes [5]. For lack of alternative treatments, often the cessation of the hydroxyurea treatment is not possible. We report this case to subscribe the potential muco-cutaneous side-effects of hydroxyurea therapy and to increase clinical awareness of the problem.

The symptomatic oral lesions may need for dose reduction or treatment withdrawal and these approaches lead to resolution of the lesions or symptom improvement [2]. In our case, mucosal lesions were important factor for changing therapy of hydroxyurea. Patients with myeloproliferative disorders, undergoing hydroxyurea therapy, should have oral examination prior and during the therapy. In the other hand, presence of oral lesions may be an indication for dose reduction, discontinuation or replacement of therapy. Finally, the purpose of this case report is pointed that hydroxyurea can provoke oral lesions and mucositis and could be a delay in early detection of oral SCC and clinicians must be aware of this.

REFERENCES

1. De Benedittis M, Petruzzi M, Giardina C, Lo Muzio L, Favia G, Serpico R. Oral squamous cell carcinoma during long-term treatment with hydroxyurea. *Clinical and experimental dermatology*. 2004 Nov 1;29(6):605-7.
2. Mendonça R, Gueiros LA, Capellaro K, Pinheiro VR, Lopes MA. Oral lesions associated with hydroxyurea treatment. *Indian Journal of Dental Research*. 2011 Nov 1;22(6):869.
3. Young HS, Khan AS, Kendra JR, Coulson IH. The cutaneous side-effects of hydroxyurea. *Clinical & Laboratory Haematology*. 2000 Aug 1;22(4):229-32.
4. Hartmann K, Nagel S, Erichsen T, Rabe E, Grips KH, Bieber T, Pannier-Fischer F. Cutaneous ulcers following hydroxyurea therapy. *Phlebologie*. 2004 Dec 1;33(6):202-5.
5. Vassallo C, Passamonti F, Merante S, Ardigo M, Nolli G, Mangiacavalli S, Borroni G. Muco-cutaneous changes during long-term therapy with hydroxyurea in chronic myeloid leukaemia. *Clinical and experimental dermatology*. 2001 Mar 1;26(2):141-8.
6. Sanchez-Palacios C, Guitart J. Hydroxyurea-associated squamous dysplasia. *Journal of the American Academy of Dermatology*. 2004 Aug 31;51(2):293-300.
7. Pamuk GE, Turgut B, Vural Ö, Demir M, Tek M, Altaner Ş. Metastatic squamous cell carcinoma of the skin in chronic myeloid leukaemia: complication of hydroxyurea therapy. *Clinical & Laboratory Haematology*. 2003 Oct 1;25(5):329-31.
8. Daoud MS, Gibson LE, Pittelkow MR. Hydroxyurea dermopathy: a unique lichenoid eruption complicating long-term therapy with hydroxyurea. *Journal of the American Academy of Dermatology*. 1997 Feb 28;36(2):178-82.
9. Saraceno R, Teoli M, Chimenti S. Hydroxyurea associated with concomitant occurrence of diffuse longitudinal melanonychia and multiple squamous cell carcinomas in an elderly subject. *Clinical therapeutics*. 2008 Jul 1;30(7):1324-9.
10. Papi M, Didona B, DePità O, Abruzzese E, Stasi R, Papa G, Cavalieri R. Multiple skin tumors on light-exposed areas during long-term treatment with hydroxyurea. *Journal of the American Academy of Dermatology*. 1993 Mar 1;28(3):485-6.