

Cutaneous effects after prolonged use of hydroxyurea in Polycythemia Vera *

Efeitos colaterais cutâneos após uso prolongado de hidroxiuréia na Policitemia Vera

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Abstract: Hydroxyurea is an hydroxylated urea derivative used in many myeloproliferative disorders. Many, but unusual cutaneous disorders are related after its prolonged use. Their pathogenesis is not clear, but it is suggested that there is direct toxicity of the drug on the skin. We described a white, 75-year old man with diagnosis of Polycythemia Vera that in 11 years of treatment developed many cutaneous lesions: skin hyperpigmentation, atrophic lesions on forearms, longitudinal melanonychia of 20 nails, right forearm ulcer, cutaneous xerosis, ichthyosis and auricular spinocellular carcinoma. At this moment, the literature reports describe little diversity of lesions in affected patients.

Keywords: Hydroxyurea; Polycythemia vera; Skin manifestations

Resumo: A hidroxiureia é um derivado hidroxilado da ureia utilizado em diversas desordens hematológicas. Inúmeras alterações cutâneas, porém raras, são relatadas após seu uso prolongado. A patogênese das mesmas não está bem esclarecida, porém, sugere-se que a droga tenha uma ação tóxica direta sobre a pele. Descrevemos um homem de 75 anos, branco, com diagnóstico de Policitemia Vera que, ao longo de 11 anos de tratamento com hidroxiureia, evoluiu com várias lesões cutâneas: hiperpigmentação da pele, lesões atróficas em antebraços, melanoníquia longitudinal das 20 unhas, úlcera em antebraço direito, xerose cutânea, ictiose em pernas e carcinoma espinocelular no pavilhão auricular direito. Até o momento, os relatos na literatura descrevem pouca diversidade de lesões nos pacientes acometidos.

Palavras-chave: Hidroxiuréia; Manifestações cutâneas; Policitemia vera

INTRODUCTION

Hydroxyurea is a chemotherapeutic agent used in the treatment of several hematological diseases. Innumerable, although rare, are the skin alterations associated with their use.¹⁻³ Usually they are found in small numbers, on the same patient. Among the observed manifestations are: cutaneous xerosis, diffuse skin hyperpigmentation, ungueal alterations, dermatomyositis-like lesions, ulcerous lesions and even skin carcinomas.⁴⁻⁸ The pathogenesis for such alterations is still not well clarified and there are several hypotheses being currently examined. The onset of several and rare adverse mucous-cutaneous and ungueal reactions in the same patient is reported here,

some of them with atypical presentation, during prolonged use of hydroxyurea in the treatment of Polycythemia Vera.

CASE REPORT

In January of 1996, a 64-year old man of mixed race, from Floresta - PE was referred to the hematology service because his blood tests had laboratory findings of polyglobulia, with 74% hematocrit, splenomegaly and facial plethora. There were no lymphadenomegalies or hemorrhage signs and the karyogram was normal. The diagnosis was Polycythemia Vera and the treatment was started with hydroxyurea,

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adjusted to between 0.5 and 1.5g/day, according to hematimetric levels, with the objective of maintaining hematocrit percentage below 50%.

After eleven years of treatment, the patient had numerous skin lesions that appeared gradually: diffuse skin hyperpigmentation, atrophic lesions on forearms, longitudinal melanonychia of 20 nails, diffuse cutaneous xerosis, ichthyosiform lesions on legs, ulcer on right forearm and the onset of a well-differentiated squamous cells carcinoma on the upper third of the right outer ear. The lesion was surgically excised and later confirmed by histological exam, 10 years after the drug began to be used (Figures 1, 2 and 3).

The patient began to be jointly followed by dermatology and hematology specialists and in view of the severity of the basic disease, it was decided to maintain therapy with hydroxyurea associated with photoprotection and topical care for the forearm ulcer, which increased in size, inducing to suspension of the antitumoral agent and use of phlebotomy in the treatment of Polycythemia Vera.

After the drug was suspended, the ulcerous lesions and melanonychia regressed (Figures 4, 5 and 6). The patient later died of acute myocardial infarction.

DISCUSSÃO

Hydroxyurea is an hydroxylated urea derivative that has been used in the treatment of many hematological disorders such as Chronic Myeloid Leukemia, Polycythemia Vera, Essential Thrombocytemia, Thalassemia and Sickle-cell Disease.^{3,6} More recently, it has been used as alternative in severe cases of refractory Psoriasis and as an adjuvant in HIV infection.^{7,9,10}

This chemotherapeutic agent blocks the conversion of ribonucleotides into desoxyribonu-



FIGURE 2: Melanonychia on right hand

cleotides when it inhibits M2 subunit of ribonucleotide reductase. Consequently, it interferes in DNA synthesis of proliferative cells, leading them to death in the S phase of cell cycle.⁶

It is normally a well-tolerated drug in usual doses, with rare serious side effects. Among the possible mucocutaneous complications are: xerosis, diffuse hyperpigmentation of the skin and oropharyngeal mucosa, alopecia, erythema, nail alterations (melanonychia, onycholysis, blue lunula), palmoplantar keratoderma, dermatomyositis-like lesions, stomatitis and aphthoid ulcers. More severe adverse effects include leg ulcers and skin carcinomas (basal and squamous cells).^{3,5,7,11-13}

The pathogenesis of skin alterations induced by hydroxyurea is still not well understood. It is believed that leg ulcers develop as a consequence of the decrease of blood flow in microcirculation and anox-



FIGURE 1: Ulcer on right forearm



FIGURE 3: Melanonychia on right foot



FIGURE 4: Ulcer healed after suspension of hydroxyurea

ia secondary to macrocytosis induced by the drug.⁶ There seems to be a platelet deregulation associated with these factors, with microthrombosis formation and loss of tissue repair by direct toxic action of the drug.⁴

The basic disease seems to influence the risk for ulcer development, which may be evident in around 9% of patients undergoing treatment for Myelodysplastic Diseases and in 29% of Sickle-Cell Disease carriers.^{4,12} The ulcers are located almost exclusively in areas of leg trauma and affect more frequently elderly women (65% of cases), who have been using the drug for at least one year.¹² Studies reveal that spontaneous healing of ulcerated lesions occur during the period from eight weeks to nine months after suspension of the drug.^{1,2,12} Haniffa *et al.*¹ and Neynaber *et al.*⁵ advocate topical care and dose reduction, preferring to withdraw hydroxyurea administration only in refractory cases. In the report-



FIGURE 5: Melanonychia on right hand after suspension of drug



FIGURE 6: Decrease of melanonychia on right foot after suspension of hydroxyurea

ed case, contrary to the described, the patient is male and presented ulcer of atypical localization (forearm). We believe there is a connection between the onset of the ulcerated lesion and administration of the drug, since after it was suspended the lesion regressed.

Several hypotheses have been suggested for the pathogenesis of hyperpigmentation of skin, mucosa and nails induced by hydroxyurea. It is believed that genetic predisposition, photosensitization, focal stimulation of melanocytes and the toxic effect on unguinal bed and matrix are involved.^{12,14} The more probable hypothesis seems to be the increase in melanin production by direct activation of melanocytes by the drug. A review of English literature revealed that cutaneous hyperpigmentation without unguinal infection is more common, and the isolated presence of melanonychia is rare.¹² Adult and black patients, as well as those with basic sickle-cell disease are more predisposed to pigmentary alterations caused by hydroxyurea.¹⁴

The most usually found unguinal findings are longitudinal bands of variable pigment intensity, normally on just a few nails, mainly fingernails. The literature reports only four cases where 20 nails were involved in the same patient, which was also observed in the present reported case.⁵ Other patterns have already been described, such as transverse bands and their diffuse pigmentation, which may occur simultaneously in the same patient. In a previous study, it was observed that the risk for melanonychia in patients receiving hydroxyurea therapy was 4%, most of them women and after a long period of treatment.⁵ A few months after suspension of the drug, the pigmentary alterations tend to resolve.

After 10 years of hydroxyurea treatment, the patient developed an histologically well-differentiated spinocellular carcinoma on the helix of the right outer

ear. Among the most severe adverse effects of hydroxyurea is the development of skin carcinomas, usually after a long period of treatment with the drug.^{8,13} A theory is posed that there is mutagenic potential of the chemotherapeutic agent for carcinogenesis and action as inhibitor of DNA repair mechanisms after damage caused by external factors (i.e. ultraviolet radiation).^{5,7}

A direct cumulative damage, as well as a cytotoxic effect of hydroxyurea on basal keratinocytes, resulting in atrophic skin lesion has also been proposed.³ In the case of our patient it became evident that, with the passing of time, numerous atrophic lesions appeared, more pronounced on the forearms and back of hands. Other cutaneous adverse reactions reported in the literature as secondary to the prolonged use of the drug, such as cutaneous xerosis and ichthyosiform lesions were also observed in this case.

The fact that the studied patient died of acute myocardial infarction may be related to thrombotic events to which individuals with Polycythemia Vera may be exposed.¹⁵

In synthesis, the present report finds numerous ungueal and cutaneous adverse reactions in a single patient, as a result of prolonged therapy with hydroxyurea. As it is a frequently used drug, we alert the specialists to the need of special attention to these possible alterations, by offering early diagnosis and treatment. □

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