



## Squamous Cell Carcinoma Accompanying Chronic Myeloid Leukemia: Case Report and Review of the Literature

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Başvuru Tarihi: 24.08.2011,  
Kabul Tarihi: 18.01.2012



DOI:  
10.7247/jiumf.2012.19.1.40\_45

**Background:** Chronic Myelogenous Leukemia (CML) is a myeloproliferative disorder characterized by, overproduction of myeloid cells. Hydroxyurea is an antimetabolite which is commonly used in myeloproliferative syndromes. Reported skin changes related to hydroxyurea therapy may range from xerosis to mucocutaneous cancers.

**Aim:** In this study, our aim was to understand and discuss the underlying reason for the development of squamous cell carcinoma (SCC) in patients receiving hydroxyurea and present a case, in whom we operated to excise the tumoral masses and reconstruct them.

**Materials and Methods:** After receiving hydroxyurea therapy for four years, the patient was diagnosed as squamous cell carcinoma on the upper lip and, on the dorsum of the left hand. She was operated and the tumoral masses were excised. The lesion on the upper lip was reconstructed with nasolabial flap, inner and inferior sides of the flap was skin grafted. The defect on the dorsum of the hand was skin grafted.

**Results:** No complication related to operation occurred. Throughout postoperative eight months of follow-up period, the patient had no complaint regarding the operation.

**Conclusion:** Skin lesions of patients receiving hydroxyurea therapy must be carefully examined and monitored regularly, since these lesions may proceed to skin cancers.

**Key Words:** Chronic Myelogenous Leukemia; Hydroxyurea; Squamous Cell Carcinoma; Flap; Graft.

### Kronik Miyeloid Lökemi'ye Eşlik Eden Skuamoz Hücreli Karsinom: Olgu Sunumu ve Literatür Taraması

**Giriş:** Kronik Miyeloid Lösemi (KML), miyeloid hücrelerin aşırı üretimi ile karakterize miyeloproliferatif bir hastalıktır. Hidroksiüre de miyeloproliferatif sendromlarda sıklıkla kullanılan bir antimetabolit ilaçtır. Hidroksiüre tedavisine bağlı olarak bildirilen cilt değişiklikleri kserezizsten mukokutanöz kanserlere kadar çeşitlilik gösterir.

**Amaç:** Bu çalışmada amacımız, hidroksiüre tedavisi alan hastalarda skuamoz hücreli karsinom gelişiminin altta yatan sebeplerini anlamak, tartışmak ve tümör eksizyonu ve rekonstruksiyonu yaptığımız böyle bir hastayı sunmaktır.

**Meteryal ve Metod:** Üst dudak ve sol el dorsumunda skuamoz hücreli karsinom tanısı almış olan hasta dört yıldır hidroksiüre tedavisi almaktaymış. Bu hasta opere edilerek tümöral kitleleri eksize edildi ve üst dudakta oluşan defekt iç ve alt tarafları greflenen nasolabial flep ile rekonstruktö edildi. El dorsumunda oluşan defekt ise cilt grefti ile kapatıldı.

**Bulgular:** Yapılan operasyona bağlı bir komplikasyon ile karşılaşmadı. Postoperatif sekiz aylık takip döneminde hastanın operasyona bağlı bir şikayeti olmadı.

**Sonuç:** Hidroksiüre tedavisi alan hastaların cilt lezyonları cilt kanserine ilerleyebileceğinden dolayı dikkatli bir şekilde muayene edilmeli ve düzenli olarak takip edilmelidir.

**Anahtar Kelimeler:** Kronik Miyeloid Lösemi; Hidroksiüre; Skuamoz Hücreli Karsinom; Flep; Greft.

### Introduction

Hydroxyurea is an antimetabolite which is commonly used in myeloproliferative syndromes such as Chronic

Myelogenous Leukemia (CML), polycythaemia vera, myelofibrosis, sickle cell anemia, and idiopathic thrombocytosis. It is considered as a first choice treatment for chronic myelogenous leukemia, in which dosages ranging from 500 to 1500 mg daily have proved to be highly effective for induction and maintenance of remission.<sup>1</sup> Secondary to hydroxyurea use patients may develop cutaneous changes. These changes may vary from xerosis to mucocutaneous cancers. Cutaneous changes related to hydroxyurea treatment that are

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reported include partial alopecia, dryness and atrophy of skin and subcutaneous tissue, skin and nail hyperpigmentation and lower leg ulcers.<sup>2-5</sup> The dorsal aspect of hands and fingers may present a poikilodermatous eruption with atrophy, erythema and scaling which has been characterized as 'hydroxyurea dermopathy'.<sup>6-8</sup> The occurrence of actinic keratosis has been reported in some patients treated with long term hydroxyurea therapy for chronic myelogenous leukemia.<sup>9-10</sup>

Our aim in this study was to present a case how we operated to excise the squamous cell carcinomas on the upper lip and dorsum of the hand and reconstruct them. At the same time, we tried to understand review and discuss the underlying reasons average time needed for the development of squamous cell carcinoma in patients receiving hydroxyurea. Therefore, our main goal was to inform and avoid the patients from the facilitating factors for the development of squamous cell carcinomas in patients who are treated with hydroxyurea.

### Case Report

After receiving hydroxyurea therapy for four years, in April 2005, a 67-year-old woman presented with a 2x2.3 cm tumoral mass on the dorsum of the left hand and 1.8x3 cm tumoral mass on the upper lip (Figures 1-3). She had been diagnosed as chronic myeloid leukaemia (CML) in April 2001. Since then (48 months) she had been treated with hydroxyurea at a dose of 1500 mg/day (3x500 mg). On admittance, white blood count:  $25.5 \times 10^3/\text{ul}$ , neutrophil count:  $21.7 \times 10^3/\text{ul}$ , lymphocyte count:  $1 \times 10^3/\text{ul}$ , lymphocyte percent: 3.8%, neutrophil percent: 85.1%, red blood cell count:  $1.98 \times 10^6/\text{microliter}$  and Hemoglobin was 6,3 gr/dl. On admittance, she presented with hyperpigmented lesions on nose and both cheeks, skin atrophy, ulcerated lesions on feet, actinic keratosis on chin, poikilodermatous changes over the dorsum of the hands, generalized xerosis and skin atrophy. On the upper lip, 1.8x3 cm of ulcerated tumoral lesion with sharp edges was observed. At the same time, on the dorsum of the left hand, another lesion with 2x2.3 cm of dimensions and of similar physical characteristics were observed. Because punch biopsy obtained from these ulcerated lesions on upper lip and dorsum of the left hand revealed, squamous cell carcinoma, total excision and reconstruction was planned.

Because punch biopsy obtained from these ulcerated lesions on upper lip and dorsum of the left hand revealed squamous cell carcinoma, total excision and reconstruction was planned. The tumor on the left hand was excised with a 1 cm of security margin. The formed defect on the dorsum of the left hand was

reconstructed with a full thickness skin graft, harvested from the suprapubic area. Then, the tumor on the upper lip was excised with 1 cm of security margin. 80% of the upper lip was excised. The superior margin of the defect was reached the columellar base. After the excision of the tumor, the formed defect was reconstructed with a left-sided, inferior-based nasolabial local transposition flap. The inner and inferior parts of the transposed nasolabial flap were grafted with full thickness skin. (Figures 4,5). The operation was terminated without complication.



**Figure 1.** Preoperative view of the patient with a tumoral mass on the dorsum of the left hand and upper lip.



**Figure 2.** Preoperative view of the skin tumor on the upper lip (Xerosis, atrophic skin and hyperpigmented lesions are seen).



**Figure 3.** Preoperative view of mass on the dorsum of the left hand.



**Figure 4.** Intraoperative view of the defect formed after tumor excision and design of flap.



**Figure 5.** Intraoperative view after flep adaptation.

## Results

The patient had no postoperative complication. Infection, hematoma formation, seroma formation, circulatory disturbances of flap, or partial or total flap loss, problems related to graft take did not occur. Throughout postoperative eight months of follow-up period, the patient had no complaint related with the operation and did not need any revisional surgery. Postoperatively, oral sphincter functional insufficiency was not present (Figure 6).

In the first postoperative week the patient was offered to intake liquid, second postoperative week to intake semi-solid foods. Following every meal, gargling was suggested to the patient. After postoperative two weeks the patient could feed freely, without any limitation. Solid or liquid food intake was not problematic. After eight months of follow up, the patient did not visit our clinic for controls.



**Figure 6.** Postoperative view after eight months.

## Discussion

As a myeloproliferative disorder CML is characterized by overproduction of myeloid cells.<sup>11</sup> Adult CML onsets after 3 years of age.<sup>12</sup> Generally, the disease remains stable for years which then transforms to a more malignant disease.<sup>11</sup>

CML is associated with a reciprocal transformation between the long arms of chromosomes 9 and 22, so called Philadelphia chromosome.<sup>11</sup> A large portion of 22q is translocated to 9q and a small piece of 9q (contains abl)

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is translocated to 22q and is received at a specific site called breakpoint cluster (bcr).<sup>11</sup>

Adult CML presents with nonspecific constitutional complaints such as, fatigue, low grade fever and night sweats, and findings such as massive splenomegaly and hepatomegaly.<sup>12</sup> At the time of diagnosis, Philadelphia chromosome-positive clone dominates and mostly is the only detectable finding.<sup>11</sup> Since early CML does not behave like a malignant disease, despite some qualitative abnormalities (low leucocyte alkaline phosphatase), white blood cells differentiate and the neutrophils combat infection normally, thus normal bone marrow function is sustained.<sup>11</sup> Later disease progresses to accelerated phase and finally to blast crisis.<sup>11</sup> There is another form, so called juvenile form of chronic myelogenous leukemia which onsets under two years of age and is Philadelphia chromosome negative.<sup>12</sup> The juvenile form onsets with eczematoid skin rash, marked lymphadenopathy, tendency to bleed and, moderate hepatosplenomegaly.<sup>12</sup>

Single drug chemotherapy (hydroxyurea or busulfan) can be used for the treatment of adult CML, but the accelerated and blast phases are refractory to drug therapy.<sup>12</sup> As in the case we present here in this article, hydroxyurea therapy is commonly used for the CML treatment. Bone marrow transplantation is the only known cure.<sup>12</sup> Although the long term results are not yet known, alpha interferon has shown promising results by reducing or eliminating the Philadelphia chromosome-positive malignant clone.<sup>12</sup>

Hydroxyurea is a hydroxylated molecule of urea. It was first synthesized in 1869 by Dresler and Stein.<sup>13</sup> Hydroxyurea inhibits DNA synthesis by blocking diphosphate ribonucleotide reductase and DNA thymidine uptake.<sup>14</sup> Hydroxyurea causes side effects such as, bone marrow depression, blood count changes, erythrocyte abnormalities, skin rashes, erythema, somnia, stomatitis, anorexia, nausea, vomiting and diarrhea.

Cancers such as squamous cell carcinomas and basal cell carcinomas are the most important manifestations of hydroxyurea therapy among other cutaneous manifestations.<sup>15</sup> Hydroxyurea, has been shown to induce chromosomal damage and inhibition of DNA repair in ultraviolet (UV) irradiated human cells in vitro environment.<sup>16,17</sup> Therefore it is being thought that, hydroxyurea may interfere with cell replication in the basal layer of epidermis.<sup>8</sup> Thus, in patients receiving long term hydroxyurea therapy, the development of squamous and basal cell carcinomas does not seem to be occasional.<sup>18</sup>

Ultraviolet rays are thought to play an important role in

hydroxyurea-induced impairment of DNA repair. Location of the lesions in light exposed areas is due to a mechanism that can be described as 'Xeroderma Pigmentosum-like'.<sup>19</sup> In addition to the impairment in DNA repair, Hydroxyurea is likely to interfere with DNA synthesis inducing chromosomal damage and as demonstrated by Francis et al, inhibits DNA repair in ultraviolet exposed human cells.<sup>17</sup> So, it disrupts the normal replication and repair mechanism of healthy cells causing secondary carcinogenesis. Interaction of immunosuppression and malfunctioning of natural killer cells, which is a typical finding in chronic myelogenous leukemia can be added.<sup>20</sup> It is also reported that hydroxyurea has intrinsic mutagenic activity.<sup>21</sup> Since Hydroxyurea therapy is a commonly used treatment modality in CML, the patients with CML can also present with such clinical findings as others, who are receiving hydroxyurea therapy.

In a study by Vasallo et al, mucocutaneous changes related to long term therapy with hydroxyurea in CML were listed.<sup>21</sup> In this study, the frequency and clinical variety of severe cutaneous and mucosal side effects of long term hydroxyurea therapy was observed in a group of 21 out of 158 patients (13%) affected by chronic myelogenous leukemia. The median age was 58 years (range 25-79 years) with male to female ratio of 3.5:1. Patients received hydroxyurea therapy for a median period of 38 months (range 7-120 months). The induction dose of hydroxyurea was 1500-2000 mg/day orally until response. Maintenance dose varied between 500 and 1000 mg/day according to response. While severe skin atrophy was characteristic in all 21 patients, diffuse or localised cutaneous hyperpigmentation was present in half of the patients. In addition they listed all the cutaneous changes they observed in 21 patients who had severe skin atrophy. The cutaneous changes that Vasallo et al have reported include; acral erythema (in all 21 patients), xerosis (in 19 patients), ichthyosiform lesions (in 16 patients), telangiectasies (in 16 patients), malleolar ulcers (in 13 patients), heel ulcers (in 1, patient), oral mucosa ulcers (in 1 patient), glans penis ulcers (in 1 patient), dermatomyositis-like changes (in 7 patients), hyperpigmentation (in 10 patients), squamous cell carcinoma (in 3 patients), livedoid fixed erythema of heels (in 6 patients), glossitis (in 2 patients), upper lip (in 1 patient) and lower lip (in 1 patient) ulcers, scrotum ulcers (in 1 patient), keratoacantomias (in 2 patients), stomatitis (in 4 patients), vasculitis (in 1 patient), ulcer on the toes (in 1 patient).<sup>21</sup> Because of severe mucocutaneous changes, hydroxyurea was discontinued in all patients. Among neoplastic lesions three squamous cell carcinomas (on lower lip, left auricle and forehead), and two keratoacantomias (on left cheek and dorsum of right hand) were observed. The patients who developed these squamous cell neoplasms, had received hydroxyurea therapy for the median time of 76.5

months (range 60-120 months) but the cumulative dose was not available. None of the patients developed metastases<sup>(21)</sup>.

Since hydroxyurea therapy can provoke oral ulcers and mucositis,<sup>21</sup> a delay in early detection of oral squamous cell carcinomas can happen as in the case of MDe Benedditis et al. thus, clinicians must be well aware of this.<sup>22</sup> MDe Benedditis et al. reported a polycythemia vera case, who developed oral squamous cell carcinoma without any known risk factors, after receiving a cumulative dose of 6255 grams of hydroxyurea therapy throughout 15 years.<sup>22</sup> Oral squamous cell carcinoma secondary to hydroxyurea therapy occurs after more prolonged treatment with higher cumulative doses of hydroxyurea than happens with skin tumors. This may be due to the fact that oral mucosa, unlike skin, is not exposed to chronic ultraviolet irradiation.<sup>22</sup>

In our case, the patient received hydroxyurea therapy for 48 months at a dose of 1500 mg (3x500mg) daily. Best et al (1998) reported two cases with myeloproliferative diseases who developed multiple skin cancers after long term therapy with hydroxyurea which the cumulative dose was 3958 grams.<sup>15</sup> Papi et al (1993) reported the appearance of multiple squamous cell carcinomas and basal cell carcinomas in an old age patient with CML treated with hydroxyurea for 1.5 years with a cumulative dose of 1825 grams.<sup>9</sup> Esteve et al has reported an 83 year old woman receiving long term (2 years) hydroxyurea with a cumulative dose of 4745 grams for polycythemia vera, with synchronous multiple cutaneous and oral squamous cell carcinomas.<sup>23</sup>

MDe Benedditis et al listed 23 available reported cases in literature with cutaneous squamous and basal cell carcinomas and oral cancer which were affected by CML essential thrombocytopenia and polycythemia vera who received long term therapy with hydroxyurea mentioning their underlying diseases, ages, duration and cumulative dose of treatment with hydroxyurea.<sup>22</sup> When we evaluate this list, we see variable cumulative doses of hydroxyurea, and variable duration of treatment with hydroxyurea. This result tells us that, age of the patient, history of the patient, like smoking and, risk factors, like UV rays, sun exposure and, other variables must be important additional factors in determining the time when skin or oral malignancies will develop. Benedditis et. al. report that a causal relationship between long term hydroxyurea treatment and oral cancer may be speculated on the basis of at least three absolute criteria for causation:<sup>24</sup> a) the long lasting presence of a well known mutagenic agent; b) the frequently observed cutaneous carcinomas in patients who are treated with hydroxyurea and the possible similar actions of hydroxyurea on skin and oral mucosa as shown by the

arising of painful ulcers for both.<sup>21</sup> c) absence of local or systemic factors.<sup>22</sup>

## Conclusion

Since hydroxyurea therapy is a commonly used treatment modality in CML, the patients with CML can also present with such clinical findings as others, who are receiving hydroxyurea therapy. We diagnosed squamous cell carcinoma in a CML case, receiving hydroxyurea therapy. As we reviewed the literature for similar cases, we have seen few other reported cases who were treated with hydroxyurea and developed squamous cell carcinomas and other skin lesions. Even if benign, the physicians examining skin lesions of patients who are treated with hydroxyurea, must be careful during physical examination, as these lesions may proceed to skin cancers. Malign skin tumors may arise as early as 1.5-2 years after the initiation of hydroxyurea therapy.<sup>9,23</sup> For this reason, these lesions must be photographed on each follow-up, thus comparison may be done. Hydroxyurea therapy replacement with another drug may be offered to the hematology clinic if any suspicious squamous cell carcinoma or basal cell carcinoma lesions appear. The dermatologists, plastic surgeons and physicians who administer hydroxyurea, must keep in mind the cutaneous side effects of hydroxyurea. Those patients must be monitored regularly for skin lesions. We recommend continuous protection against UV rays and sun exposure, as these patients are more vulnerable to develop skin cancers than normal population. But protection against sun exposure is not enough to feel safe for the development of skin cancers in patients receiving hydroxyurea. From this, we understand that sun exposure is only one of the factors which facilitate the development of skin cancer. The age of the patient, history of the patient, like smoking, and risk factors, like UV rays, sun exposure, and other variables must be other important additional factors in determining the time when skin or oral malignancies will develop.

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**How to cite this case report:** Kılınc H, Tenekeci G, Bilen BT. Squamous Cell Carcinoma Accompanying Chronic Myeloid Leukemia: Case Report and Review of the Literature. *JJUMF* 2012; 19(1): 40-5. DOI: 10.7247/jjumf.2012.19.1.40\_45