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Oral and Skin Pigmentations associated with hydroxyurea therapeutic doses in a patient with sickle cell disease: Case Report

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ABSTRACT

Hydroxyurea is an effective treatment for Sickle cell disease. Hydroxyurea has classified as an antineoplastic agent and is also prescribed as Antisickling agent; it works through inhibition of DNA synthesis at S phase. Despite Hydroxyurea benefits sickle cell patients, undesirable side effect such as leukopenia and hyperpigmentation were observed. Hydroxyurea-induced hyperpigmentation is mainly seen in the skin and rarely in the oral cavity. Although Hydroxyrea-induced pigmentation is benign and reversible, this mild pathological condition should have considered.

فرط التصبغ في تجويف الفم و الجلد الناتج من العلاج بالهيدروكسي يوريا في مرضي فقر الدم المنجلي

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الكلمات المفتاحية:
فقر الدم المنجلي
هيدروكسي يوريا
فرط تسبغ
تجويف الفم

الملخص

يعتبر هيدروكسي يوريا علاجا فعالا لمرض فقر الدم المنجلي.وقد صنف هيدروكسي يوريا كدواء لعلاج الأورام و يتم وصفه ايضا كعقار مضاد لتمنجل كرات الدم الحمر. آلية عمل هذا الدواء تكمن في تثبيط عملية نسخ الحمض النووي في مرحلة الانقسام الخلوي.رغم أهمية هذا الدواء لمرض فقر الدم المنجلي إلا أن بعض أعراض جانبية غير مرغوب فيها مثل انخفاض عدد كرات الدم البيض و فرط تصبغ تظهر مع تناول هذا الدواء. فرط التصبغ الناتج عن تناول هيدروكسي يوريا يلاحظ عادة في الجلد و نادرا ما يشاهد في الغشاء المخاطي لتجويف الفم.وبرغم فرط التصبغ الناتج عن تناول هيدروكسي يوريا يعتبر عرضا حميدا و يرجع لون البشرة لطبيعته عند إيقاف الدواء إلا أن هذا التغير المرضي البسيط يجب أن يوضع في الإعتبار بلا استهانة.

I. Introduction

Sickle cell anemia is a hereditary blood disorder accompanied with abnormal hemoglobin formation known as sickle hemoglobin or hemoglobin S (HbS) within erythrocytes due to defect in beta globin gene, this gene is located on chromosome 11 (Sahoo 2017). Serious complications of the severe or acute pain in patients with sickle cell disease is ischemic in origin, and these crisis of painful condition are the most common cause for patients seeking medical attention and Hospitalization. Hemolysis also plays a central role in the pathophysiology, contributing significantly to anemia, vasculopathy, nitric oxide deficiency and inflammation (Kato et al 2009). HbS is polymerized within the erythrocyte upon deoxygenation and generates a sickle-shaped RBC which initiates the crisis (Parrow et al 2021). Hydroxyurea is the commonly used therapy for sickle cell disease, hydroxyurea exerts its effect through production of fetal haemoglobin (HbF) which is a powerful inhibitor of the HbS polymerization, Hydroxyurea inhibits ribonucleotide reductase and is categorized as an antimetabolite acting as S-phase specific cytostatic compound (Dong & McGann 2020). Although hydroxyurea is an effective drug for sickle cell disease and provides therapeutic benefit in reducing pain crisis (Ware 2010), unwished effects including black

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coloration of skin (Laughon et al 2000), oral and/or tongue pigmentation (Veillet-Lemay & Haber 2019) were observed. Hyperpigmentation has been observed in the oral mucosa, nails, and in a diffuse pattern (Aste et al 2002 & Franca et al 2011). Recently, Tansir et al 2022 reported, bluish‐black hyperpigmentation in the oral cavity mainly over the lateral borders and the ventral surface of the tongue and hypermelanotic discoloration over the surface of the nail in patient under Hydroxyurea medication. Hydroxyurea-associated intraoral hyperpigmentation (buccal mucosal at the site of mandibular right canine; at the site of maxillary central incisor and skin hyperpigmentation (hands and feet mainly the nail beds) has been reported by (Alshammasi et al 2020). Recently, patient with essential thrombocythaemia, receiving cytoreductive therapy with Hydroxyurea developed hyperpigmentation and diffuse uniform hyperpigmentation of the hands (nails) without thickening or atrophy of nails, oral mucosa was normal, and no other cutaneous lesions (Divyashree, et al. 2022),

CASE REPORT

A 43-year-old male with sickle cell disease carrying HbSS and A+ Blood Group was investigated for effects of long term use of Hydroxyurea. The patient is weighing 52 kg with 1.64 in height and body mass index of 19.3. Prior diagnosis, the patient was treated with iron tablets for several years. The disease was diagnosed in 1998 when the patient was 20 years old and hospitalized due to sickle cell crisis. After diagnosis in 1998, the patient was treated with Vitamin E for 6 months. Hydroxyurea and folic acid were introduced to the patient treatment when hospitalized again in 2003 at Tripoli Medical Centre. Dose of hydroxyurea at the beginning was 19.2 mg/kg (two capsules of 500 mg) daily, and the dose of folic acid was 5 mg/day. Dose of hydroxyurea was reduced to 9.6 mg/kg in 2009 at Royal Victoria Infirmary (RVI) in Newcastle up on Tyne, and then the patient was based again on 19.2 mg/kg of hydroxyurea daily; the patient demonstrated that the dose is not valuable. In 2016 at Leicester Royal infirmary (LRI) the patient based on dose of 96 mg/kg weekly (13.7 mg/kg daily); the medication was taken as follow; 2 daily capsules for 3 days and one daily capsule for 4 days every week. However, in 2021 a doctor at Tripoli Medical Centre has recommended to continue with 19.2 mg/kg (two capsules of 500 mg) daily.

Hydroxyurea was effective for sickle disease particularly at dose of 19.2 mg/kg per day with various effects on blood profile (table1). Increased leucocytes count with decreased Hb level by withdrawing of hydroxyurea was observed.

Periodic investigation of the patient during hydroxyurea therapy showed pigmentation of the oral mucosa of cheek and the attached gingiva (Figure 1). Moreover, pigmentation of the skin mainly on the hands and legs can be observed (Figure 2).

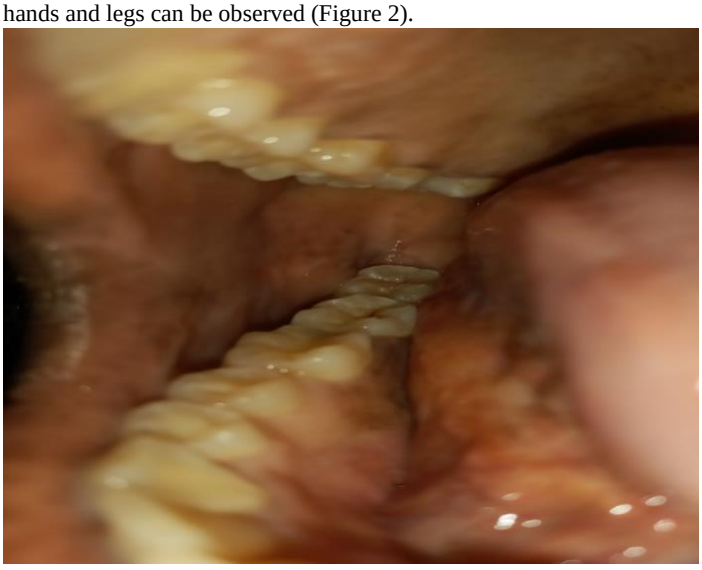

Figure 1: shows brown discoloration of mucus membrane of the oral cavity due to hydroxyurea treatment.

In addition, hyperpigmentation was also seen around the injured and healed areas of the skin.

Figure 2: shows hyperpigmentation of the healed area in hand of patient under hydroxyurea treatment.

Sensitivity to bruises and mild injuries associated with healing delay up to 2 months were observed (Figure 3). Healing is mainly occurring by second intention (Figure 4).

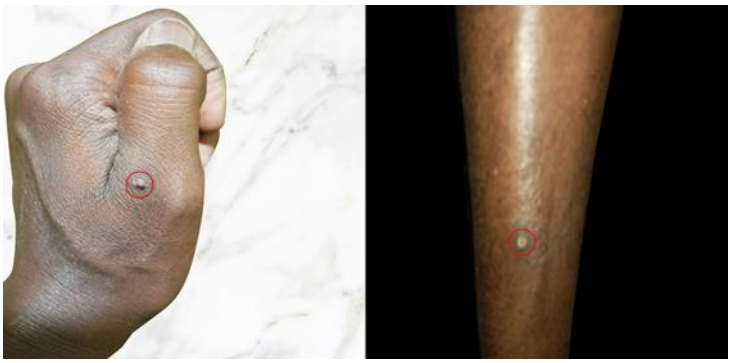

Figure 3: shows healing delays in hand and leg of sickle cell patient under hydroxyurea therapy.

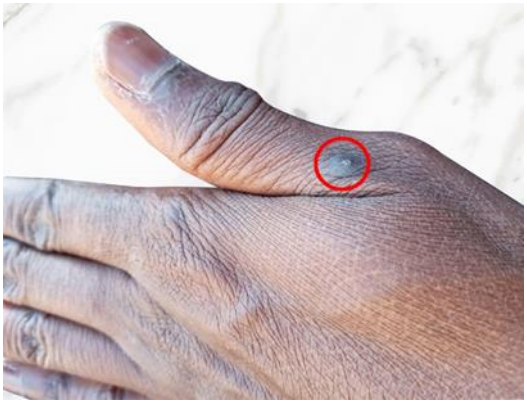

Figure 4: shows healing of wound by second intention in patient under hydroxyurea treatment

Table 1: Shows effect of hydroxyurea on normal blood parameter; suppression of myeloid cells is clear after exposure to hydroxyurea for only 4 days compared the Erythroid cells.

Blood profile after 26 days of hydroxyurea withdraw		Blood profile after 4 days of restarting of hydroxyurea treatment	
WBC	10.1 x 10^3/µl	WBC	8.4 x 10^3/µl
RBC	2.58 x10^6/µl	RBC	2.69 x10^6/µl
HB	7.7g/dl	HB	8.4g/dl
HCT	22.9%	HCT	24.8%
MCV	88.8fl	MCV	92.2fl
MCH	29.8pg	MCH	31.2pg
MCHC	33.6g/dl	MCHC	33.9g/dl
PLAT	326 x10^3/µl	PLAT	369 x10^3/µl
NEUTROPHIL	57.5%	NEUTROPHIL	56.4%
LYMPHOCYTE	33.5%	LYMPHOCYTE	43.6%

II. DISCUSSION

It has been demonstrated that Hydroxyurea has changed life of sickle cell patients and decreased their sufferings. Treatment of these patients with Hydroxurea also improves their clinical and haematological characteristics (Anie et al 2002 & McClish et al 2005). Moreover, a study by (Ballas et al 2006) reported that there was some improvement in aspects of Quality of Life in adult patients who already suffer from moderate-to-severe Sickle cell anemia.

Frequencies of vaso-occlusive crises in sickle cell patients have decreased by introducing hydroxyurea to their treatment regimens (Steinberg et at 2003).

Environmental changes including extreme cold, hot weather with huge sweating and low oxygen level have serious adverse effect on sickle cell patients. A study in Kuwait has been found that extreme climate changes such as high temperature precipitate serious complications in patients with Sickle cell anemia (Adekile 2001). In additional, numerous studies have been published all over the world showing a link between acute pain and cold temperatures from Virginia, USA (Smith et al 2003), Canada (Rogovik et al 2011) and Kuwait (Ibrahim 1980).

Hydroxyurea at dose of 19.2 mg/kg daily is a powerful protector for sickle cell patients from climate changes and low oxygen level, and makes sickle cell patients tolerated to lots of extreme environmental changes.

Previous study has also demonstrated that the effective dose of hydroxyurea ranged from 20-30 mg/kg daily with superiority of dose escalation (John et al 2020).

Dose of 96 mg/kg weekly is also beneficial but is not effective as 19.2 mg/kg daily with less tolerance to environmental changes. Treatment with 9.6 mg/kg was not effective.

Vitamin E supplement has shown a good effect on health of sickle cell patient during treatment course, (Natta et al 1980) demonstrated that vitamin E supplementation decreases percentages of irreversible sickled erythrocytes.

Despite several studies demonstrated some serious adverse effects of hydroxyurea, according to our observation toxicity of hydroxyurea looks satisfactory compared to its benefits and serious adverse effects is not expected.

(Agrawal et al 2014) has also suggested that risks of hydroxyurea are acceptable compared with the risks of untreated sickle cell disease. Majority of hydroxyurea side effect are mild and reversible presented by leukopenia, gastrointestinal disturbance and hyperpigmentation, Randi et al 2005 have also demonstrated that hydroxyurea side effects are reversible in agreement with our findings. Withdraw of Hydroxyurea showed high level of leucocyte and low RBCs and Hb, the low Hb level could be due sickle cell intravascular hemolysis.

According to our observation, myeloid suppression by hydroxyurea could give chance to erythroid lineage and lymphoid precursors to produce more RBCs and lymphocytes as reintroducing of Hydroxyurea showed increased RBC and Decreased WBC count within 4 days.

Skin Pigmentation is one of the more hydroxyurea dermatological side effects. Pigmentation is more severe in injured areas compared to the normal skin and clearly seen around the healing areas. At skin level may also appear: persistent pruritus, skin color changes (erythema, hyperpigmentation), cutaneous atrophy. Likewise, oral pigmentation, ulcerations and stomatitis may occur at mucosal level (Iancu et al 2020).

Hydroxyurea can cause direct toxicity on basal layer of the epidermis and mucosal surfaces (young et al 2000). Healing occurs by second intension or scar formation rather than first intention leading to scar formation at the healed area. It has been revealed that hydroxyurea or its metabolite can possibly form a complex with iron in hydroxyurea-induced hyperpigmentation in lower leg (Lee et al 2019), similarly observed in our study.

The incidence of hydroxyurea-induced hyperpigmentation has been reported to be as high as 50% (Cozzani et al 2015). Drug-induced hyperpigmentation has been seen as early as 7 weeks to several years after initiating hydroxyurea treatment (Karanth et al 2014).

In our study delay of healing and sensitivity to bruises and mild injuries were observed with long term use of hydroxyurea. Skin pigmentation is reversible however oral pigmentation looks permanent.

Wound healing can delay up to 2 months and over however withdraw of hydroxyurea accelerates healing. Its speculated that cutaneous atrophy induced by hydroxyurea followed by minor trauma and impaired wound healing might lead to skin ulceration (Sirieix et al 1999).

III. CONCLUSION

Introducing of hydroxyurea therapy for sickle cell disease has improved patient's health.

Hydroxyuera treatment at 19.2 mg/kg daily and Vitamin E supplements protect sickle cell patients from recurrent vaso-occlusive crises.

Despite hydroxyurea has an adverse effects including leukopenia, skin and oral hyperpigmentation, hydroxyurea therapy benefit exceed its side effects which were almost reversible.

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