Journal of Pakistan Association of Dermatologists. 2018; **28(3)**: 351-354.

Original Article

Zidovudine-induced pigmentation on skin, nail and oral cavity – a study on 119 patients

Mohammed Shoubin, Muthusamy Kandasamy, Kannan Gopalan, Seethalakshmi Ganga Vellaisamy, Navakumar Manickam

Department of Skin & STD, Vinayaka Mission Kirupanandha Variyar Medical College & Hospital, Salem, India

Abstract

Objective To assess the incidence of zidovudine induced pigmentation among HIV-infected patients.

Methods All HIV patients who were receiving antiretroviral therapy (ART) with mucocutaneous pigmentation were screened and those receiving zidovudine were included in the study. Proper mucocutaneous examination was done. Site, duration of lesions and duration of treatment were taken into consideration. All the collected data were recorded and statistically analyzed.

Results A total of 119 HIV infected patients on zidovudine were included in the study. Majority of the study population (52.9%) was on ART for more than 5 years. 114 patients were on zidovudine, lamivudine and nevirapine regimen and 5 patients were on zidovudine, lamivudine and efavirenz regimen. Pigmentation over nails was seen in 33 patients and 31 patients had both nail and oral mucosal pigmentation. Skin, nail and oral cavity pigmentation was there in 24 patients. For majority, i.e. 63 patients, nail was the first site to be involved.

Conclusion Hyperpigmentation is a major side effect with prolonged treatment of zidovudine. Prior explanation regarding adverse reactions may improve outcome of the therapy, as well as, adherence to the antiviral drug regimen.

Key words
Zidovudine, pigmentation, zidovudine-induced pigmentation, HIV.

Introduction

For cutaneous hyperpigmentation drugs can be the causative agents in 10-20% of cases with frequently involved drugs being nonsteroidal anti-inflammatory drugs, antimalarials, amiodarone, chemotherapeutic agents, psychotropic drugs, zidovudine, tetracyclines, and heavy metals.[1] Adverse drug reactions, drug toxicities and drug-drug interactions are an important challenge seen with highly active antiretroviral treatment (HAART) and anti-tubercular treatment.

Zidovudine, one of the first-line antiretroviral treatment regimens used to manage HIV is well documented with cutaneous and nail pigmentation in adult, as well as, pediatric HIV patients.[2,3] Nail pigmentation with zidovudine is well-documented in dark skinned individuals.[3] The pathogenesis of pigmentation and their clinical pattern vary according to the causative drug. Hyperpigmentation is usually secondary to an increase in melanin due to: (a) the stimulation of melanocytes or (b) a pigmentary incontinence developed after an unspecified cutaneous inflammation. It can also be secondary to the

Address for correspondence
Prof. Muthusamy Kandasamy, Professor and Head, Department of Skin & STD,
Vinayaka Mission's Kirupananda Variyar Medical College & Hospital, Salem-636308, India
Email: km49km@gmail.com

accumulation of the drug or its metabolites in the dermis forming complexes with melanin or iron.[4] Although the underlying pathology of nail pigmentation is not clear, in animal studies it was shown increased numbers of melanosomes within epidermal keratinocytes[5] and nail biopsy findings showed deposits of brown pigmented granules containing melanin throughout the epidermis.[6,7]

In the present study, we assessed the incidence of zidovudine-induced pigmentation among HIV-infected patients under antiretroviral treatment.

Methods

The study was conducted in the outpatient, department of Skin and STD. After screening HIV/AIDS patients for mucocutaneous and nail pigmentation, 119 patients with nail, cutaneous or oral cavity pigmentation taking zidovudine were selected who developed pigmentation after starting treatment.

Each patient was interviewed for duration of therapy, duration of pigmentation and sites involved.

Results

A total of 119 HIV-infected patients on zidovudine were included in the study. Majority of the study population (63, 52.9%) was on ART for more than 5 years. 114 (95.8%) patients were on zidovudine, lamivudine and nevirapine regimen and 5 (4.2%) patients were on zidovudine, lamivudine and efavirenz regimen. Pigmentation over nail was seen in 33 (27.7%) patients and 31 (26.1%) patients had both nail and oral mucosal pigmentation. Skin, nail and oral cavity pigmentation (**Figure 1-6**) was there in 24 (20.2%) patients. Only cutaneous pigmentation was seen in 12 (10.0%) patients. Nine patients had pigmentation over skin and nail. Three patients had pigmentation over skin and oral cavity. For majority i.e. 63 (52.9%) patients, nail was the first site to be involved, followed by oral cavity in 34 (28.6%) patients. For the remaining 22 (18.5%) patients cutaneous manifestation was observed first with 13 (10.9%) patients had facial pigmentation.

Duration of lesions was there up to 4 years in 81 (68.1%) patients. The remaining 38 (31.9%) patients were not exactly aware of duration of lesions, but they confirm the fact that pigmentation developed after starting treatment.

Discussion

In our study nails were involved in most number of patients. Nail pigmentation with zidovudine is mainly seen in dark skinned individuals and it seems to be reversible. Both doctors and patients should be aware about this common side effect so that unnecessary investigations can be avoided.

Table 1 Duration of treatment (n=119).

Duration (years)	*N (%)*
0-2 years	4 (3.4)
2-5 years	41 (34.4)
5-10 years	63 (52.9)
>10 years	11 (9.3)

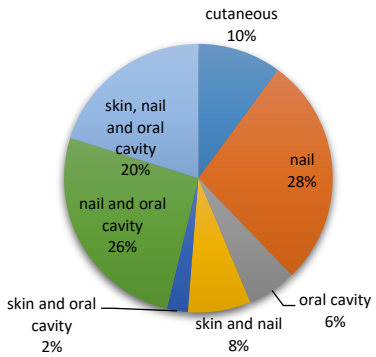

Figure 1 Sites involved (n=119).

Figure 2 Pigmentation over tongue and face.

Figure 3 Pigmentation over both upper limbs.

Figure 4 Pigmentation over nails.

Figure 5 Pigmentation over nails.

Figure 6 Pigmentation over palms.

Longitudinal melanonychia seen with zidovudine must be distinguished from the brownish hyperpigmented stripes that are seen in HIV. In zidovudine-induced pigmentation, patients would be able to appreciate that discoloration preceded or coincided with the initiation of therapy.

Greyish-black discoloration of the tongue was observed in few patients in our study, a rare side effect of zidovudine is not associated with any toxicity and is asymptomatic.[8]

Cutaneous lesions alone were observed in 12 (10.1%) patients in our study. Cutaneous lesions were seen over exposed areas of the body mainly over face and forearms.

Palmoplantar pigmentation was seen in two patients in our study. This can also be due to endocrinopathies like Addison's disease, hyperthyroidism or nutritional deficiencies like vitamin B12 deficiency. Papulosquamous eruption of secondary syphilis presenting with copper-colored pigmentation also should be ruled out.[9] Laugier-Hunziker syndrome which is characterized by flat brown marks in oral cavity and brown stripes on nails should be considered as a differential diagnosis. Diffuse hyperpigmentation over palms and soles can be seen in patients taking cyclophosphamide or doxorubicin.

Conclusion

Hyperpigmentation is a major side effect with prolonged treatment of zidovudine. Prior explanation regarding adverse reactions may improve outcome of the therapy, as well as, adherence to the antiviral drug regimen.

References

1. Dereure O. Drug-induced skin pigmentation. Epidemiology, diagnosis and treatment. *Am J Clin Dermatol*. 2001;**2**:253-62.
2. Singh SK, Rai T. A case of zidovudine induced pigmentation on palms and soles. *Indian Dermatol Online J*. 2014;**5**:98-9.
3. Chawre SM, Pore SM, Nandeshwar MB, Masood NM. Zidovudine-induced nail pigmentation in a 12- year-old boy. *Indian J Pharmacol*. 2012;**44**:801-2.
4. López-Pestaña A, Tuneu A, Lobo C, Zubizarreta J, Eguino P. Blue-black pigmentation of legs and arms in a 68-year-old woman. *Arch Dermatol*. 2007;**143**:1441-6.
5. Obuch ML, Baker G, Roth RI, Yen TS, Berger TG. Selective cutaneous hyperpigmentation in mice following zidovudine administration. *Arch Dermatol*. 1992;**128**:508-13.
6. Rahav G, Maayan S. Nail pigmentation associated with zidovudine: A review and report of a case. *Scand J Infect Dis*. 1992;**24**:557-61.
7. Grau-Massanes M, Millan F, Febrer MI, Pujol C, Alegre VA, Salavert M *et al*. Pigmented nail band and mucocutaneous pigmentation HIV positive patients treated with zidovudine. *J Am Acad Dermatol*. 1989;**21**:687-8.
8. Tadini G, D'Orso M, Cusini M, Alessi E. Oral mucosa pigmentation: A new side effect of azidothymidine therapy in patients with acquired immunodeficiency syndrome. *Arch Dermatol*. 1991;**127**:267-8.
9. Singh SK, Rai T. A case of zidovudine induced pigmentation on palms and soles. *Indian Dermatol Online J*. 2014;**5**(1):98-9.