

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Grey Finger Nails and Oral Pigmentation in HIV Infected Patients: Tool to Antiretroviral Treatment Eligibility.

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ABSTRACT

Human Immunodeficiency Virus infection is one of the major health problems worldwide. CD4+Tcell count and viral load have been used as important laboratory parameters to evaluate antiretroviral treatment eligibility. Eligibility for antiretroviral treatment in HIV infected patients is determined either by CD4 +T cell count of < 200cells/ μ l or clinical diagnosis of WHO stage 3 or 4. Since laboratory set up needed for CD4+Tcell investigations are inadequate in certain under developed countries, there is need to identify low cost clinical tools for assessing antiretroviral treatment eligibility. Hence, study was done to assess whether presence of grey finger nails and oral pigmentation in HIV positive individuals could be used to distinguish between low and high CD4+Tcell count, thus initiate antiretroviral treatment. Finger nails and oral mucosa of 50 HIV infected patients (29 cases < 200 CD4+ Tcells/ μ l, 21 patients > 200 CD4+T cells/ μ l) were photographed and evaluated. In our study we found significant co-relation ($p < 0.025$) of grey finger nails and oral pigmentation with CD4+Tcell count < 200 cells/ μ l in HIV infected patients. Though not a specific method, occurrence of grey finger nails and oral pigmentation could be a useful alternative clinical tool to assess antiretroviral treatment eligibility in resource limited settings.

Keywords: antiretroviral therapy, CD4 lymphocyte count, HIV, nails, pigmentation, mouth mucosa.

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INTRODUCTION

Human immunodeficiency virus (HIV) infection is one of the major health problems worldwide [1]. It is characterized by infection and depletion of CD4+ T lymphocytes leading to profound immunosuppression resulting in opportunistic infections, secondary neoplasms, and neurologic manifestations [2].

As of 2011, according to WHO and UNAIDS, approximately 34.2 million people have been HIV positive globally [3]. It was estimated that number of people living with HIV infection in India was approximately 2.08 million according to National Aids Control Organization (NACO) 2011 statistics. According to the United Nations 2011 AIDS report; there has been a 50% decline in the number of new HIV infections in the last 10 years in India. The states with high HIV prevalence rates include Manipur (1.40%), Andhra Pradesh (0.90%), Mizoram (0.81%), Nagaland (0.78%), Karnataka (0.63%) and Maharashtra (0.55%) [4].

The oral and perioral manifestations commonly seen in HIV infected patients include candidiasis and hairy leukoplakia, which may play a pivotal role as far as diagnosis is concerned reflecting the immune status of individual [1].

The treatment for HIV infection and its complications are complex which needs strong commitment & motivation of patient and, the resources are reasonably expensive. In a set up where CD4+Tcell testing facilities are available, Eligibility for anti-retroviral treatment (ART) for HIV infected patients is defined by the following criteria given by WHO 2003 [5].

“It is recommended to document baseline CD4 count and to offer ART to patients with

- WHO Stage IV disease, irrespective of CD4 cell count
- WHO Stage III disease (including but not restricted to HIV wasting, chronic diarrhoea of unknown etiology, prolonged fever of unknown etiology, pulmonary Tuberculosis, recurrent invasive bacterial infections or recurrent/persistent mucosal candidiasis), with consideration of using CD4 cell counts $<350/\mu\text{l}$ to assist decision-making.
- WHO Stage I or II disease with CD4 cell counts ≤ 200 cells/ μl ”
- The CD4+Tcell count and viral load have been used as the most important laboratory parameters to evaluate the course of the disease.¹ The number of circulating CD4+Tcells in normal individual usually ranges from 600 to 1600 cells/ μl and the primary signs of immunosuppression occur when CD4+Tcell count is less than 500 cells/ μl [6]. Several studies have shown a strong co-relation between oral lesions, low CD4+Tcell count and high viral load [1,10].

Since the laboratory set up needed for CD4+Tcell count investigations may not be affordable in many developing countries, there is a need to identify low cost clinical tools for assessing anti-retroviral treatment (ART) eligibility in remote places where CD4+Tcell count investigations are not available [7].

HIV infection is associated with many mucocutaneous changes or certain specific skin disease. It is now established that onychomycosis and tinea pedis are more commonly associated with HIV infection and rare cases of yellow nail syndrome have also been reported [8]. Nail and mucocutaneous pigmentation have been reported in HIV infected patients and it has been observed that there is an association of low CD4+T cell count (<200 cells/ μ l) with grey finger nails and oral pigmentation [7,10,11]. Hence the study of grey finger nails and oral pigmentation could be a screening tool to assess ART eligibility in resource limited settings.

The aim of our study was to investigate the occurrence of grey finger nails and oral pigmentation in HIV infected patients and to compare the association of grey finger nails and oral pigmentation with CD4+Tcell count in HIV infected patients.

MATERIALS AND METHODS

50 HIV positive patients, undergoing ART or yet to undergo ART at the ART centre, District Hospital, Tumkur who consented for clinical examination were randomly included in the study. Patients with dermatological conditions which can lead to nail symptoms and oral lesions which could lead to oral pigmentation, as well as severely ill HIV infected patients who were disoriented were excluded from the study.

Universal precautions for the patients and the examiners were taken into consideration during clinical examination. Patients were made to sit in a well lit area and examined for oral and nail pigmentation under natural light. Standardised Photographs of finger nails and oral cavity were taken with canon power shot SX 130 IS camera. CD4+Tcell count details were obtained from the patients records.

Two independent observers who were blinded to the patient identity and CD4+Tcell count, viewed and scored the oral and nail photographs. The scoring was done according to the following criteria: Finger nails were scored as: Normal, Grey and Indeterminate (Figure 1 A, B, C) while, the Oral mucosa was scored as: Normal, Pigmented and Indeterminate (Figure 2 A, B, C). Indeterminate group constituted conditions which lead to pigmentation or conditions which preclude clinical observations like fungal nail disease, nail varnish, oral candidiasis as well as poor photographic presentation. The inter-observer agreement was calculated using kappa statistics. The significance of association of grey finger nails and oral pigmentation with CD4+Tcell count was drawn using Chi square test.



Figure 1 : A) Normal finger nails B) Grey finger nails C) Indeterminate (fungal nail infection)



Figure 2: A) Normal oral mucosa B) Diffuse pigmentation on the tongue C) Indeterminate (Candidiasis of Tongue)

RESULTS

50 HIV positive patients examined included 15 female and 35 male subjects aged between 24-60 years. The median age of the subjects was 40 years whereas the median CD4+Tcell count was 190cells/ μ l.

18 HIV positive patients had grey finger nails along with oral pigmentation, eight patients had only grey finger nails, seven patients had only oral pigmentation, 12 patients had neither oral pigmentation, nor grey finger nails (normal) and five patients were scored as indeterminate.

The HIV positive patients were further divided into two groups based on the CD4+Tcell count and it was seen that out of 50 HIV positive patients, 29 patients had CD4+Tcell count \leq 200 cells/ μ l while 21patients had a CD4+Tcell count $>$ 200 cells/ μ l.

Out of 29 patients with CD4+Tcell count \leq 200 cells/ μ l, 16 patients had oral pigmentation and grey finger nails, five patients had only grey finger nails, three patients had only oral pigmentation, two normal appearing nail and oral mucosa and three cases were of indeterminate category. Out of 21 patients with the CD4+Tcell count $>$ 200 cells/ μ l, two patients had oral pigmentation and grey finger nails, three patients had only grey finger nails, four patients had only oral pigmentation while 10 case were normal and two were of indeterminate category.(Table 1)

Table 1: Occurrence of nail and oral pigmentation based on cd4 +t cell count among 50 HIV patients

	Patients with CD4+Tcell count \leq 200cells/ μ l Total patients : 29	Patients with CD4+Tcell count $>$ 200cells/ μ l Total patients : 21
Both oral pigmentation and grey nails	16 (55%) p< 0.025	2 (9.52%)
Only grey nails	5 (17%) p< 0.05	3 (14.2%)
Only oral pigmentation	3 (10%) p > 0.25	4 (19.4%)
Normal i.e. neither oral pigmentation nor grey nails	2 (6.8%)	10 (47%)
Indeterminate category	3	2

Statistical analysis was drawn using Chi square test. There was a good inter observer correlation of category ($k=0.51$; $P<0.05$). The presence of oral pigmentation along with grey nails was significantly associated with CD4+Tcell count ≤ 200 cells/ μl ($P< 0.025$). Patients with grey nails with no associated oral pigmentation were significantly associated with a CD4+Tcell count ≤ 200 cells/ μl ($P< 0.05$). But there was no significant association between CD4+Tcell count and oral pigmentation alone without associated grey nails ($P > 0.25$). When CD4+Tcell count was > 200 cells/ μl , neither grey nails or oral pigmentation, or both showed no significant association.

DISCUSSION

Human immunodeficiency virus is a major global threat in modern era to human species. Many manifestations of this infection in the initial stages often go unnoticed which later pronounce into an aggressive disease claiming the life of individuals. Some of the manifestations associated with oral mucosa and nails are oral pigmentation, greying of nails, onychomycosis and longitudinal melanonychia which show association with the severity of disease and immune status of individual [8].

In Industrialized countries ART guidelines recommend treatment for individuals with CD4+Tcell count ranging from 200-350cells/ μl especially in cases with factors that may limit the effectiveness of treatment on delay [9]. But in certain developing and under developed countries the facilities for CD4+Tcell count may not be available. Therefore WHO has given guidelines of using clinical staging alone or in combination with Total lymphocyte count of <1200 / μl to treat the HIV infected patients in such resource limited areas [5].

If CD4 testing is unavailable

- “WHO Stage IV disease, irrespective of total lymphocyte count.
- WHO Stage III disease (including but not restricted to HIV wasting, chronic diarrhoea of unknown etiology, prolonged fever of unknown etiology, pulmonary Tuberculosis, recurrent invasive bacterial infections or recurrent/persistent mucosal candidiasis), irrespective of the total lymphocyte count
- WHO Stage II disease with a total lymphocyte count ≤ 1200 / μl ”

In the present study, we evaluated the association of grey finger nails and oral pigmentation with CD4+Tcell count in HIV infected patients. In patients with CD4+Tcell count ≤ 200 cells/ μl , 55% of the patient showed both oral pigmentation and grey finger nails which was statistically significant ($P< 0.025$). We didn't find any significant correlation when CD4+Tcell count was >200 cells/ μl , with 47% patients not showing any grey nails nor oral pigmentation.

Hyper pigmentation of skin, oral mucosa and nails has been reported by Smith KJ et al [10]. Matthew Scarborough et al [12]. stated that compared with pink nails, grey nails were strongly associated with a CD4+Tcell count of <200 cells/ μl .

Increase in pigmentation of skin and oral mucosa could be attributed to increased release of alpha melanocyte stimulating hormone due to dysregulated release of cytokines

in HIV disease.[11]. Pigmentation could be due to melanocyte stimulating drugs like certain antivirals, antifungals, but it is also seen in patients who are not receiving antiretroviral treatment [8]. Hydroxyurea a chemotherapeutic agent used in combination with antiretroviral therapy stimulates melanocytes within the nail matrix and causes nail changes like longitudinal bands and diffused pigmentation [13]. Pigmentary changes could be due to direct toxic effect of hydroxyurea on the nail matrix basal cells or a focal stimulation of melanocytes leading to deposition of melanin in the nail matrix. Systemic chemotherapeutic agents and ingestants could also lead to discolouration of the nails [14].

A study carried out by Namakoola et al [7]. compared grey finger nails and oral pigmentation with CD4+Tcell count among HIV positive Ugandan adults showed significant correlation between grey nail and oral pigmentation with CD4+Tcell count of <200cells/ μ l.

In the present study we found significant correlation ($P < 0.025$) of grey finger nails and oral pigmentation with a CD4+Tcell count < 200 cells/ μ l for HIV infected subjects who were undergoing or yet to undergo ART. Thus we can co-relate that lower the CD4 +T cell count greater is the likelihood for nail and oral pigmentation.

CONCLUSION

Grey nails and oral pigmentation though not a specific method for identifying patients with low CD4+Tcell count could be an effective alternative clinical tool for assessment of ART eligibility in resource limited settings.

In the present study since the control patients were not included and a small sample size was selected, there is a need of study with large number of HIV infected patients with nail changes along with other prevailing systemic disease in order to come to a hypothesis which could stand our outlook.

ACKNOWLEDGMENTS

I am extremely thankful to Dr. Rudramurthy C.M.O District Hospital, Tumkur, Karnataka for providing necessary facilities and allowing me to carry out my study successfully.

I am also thankful to Dr. Prakasam (Professor) & Dr. Mahesh (Assistant professor) Department of Community Medicine, Sri Siddhartha Medical College, Tumkur, Karnataka for their help in statistical analysis.

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