

Nail Changes in Patients Infected With Human Immunodeficiency Virus

A Prospective Controlled Study

Bernard Cribier, MD, PhD; Marcello Leiva Mena, MD; David Rey, MD; Maria Partisani, MD; Vincent Fabien; Jean-Marie Lang, MD; Edouard Grosshans, MD

Objectives: To study the frequency of nail changes in a population of human immunodeficiency virus (HIV)-infected patients and to evaluate the specificity of these findings by comparison with HIV-negative control subjects.

Design: Prospective controlled study. Nail changes were recorded by a standardized clinical examination (curvature, nail plate, color, onychomycosis). In case of clinical diagnosis of onychomycosis, mycological culture was performed.

Setting: Primary care university hospital.

Patients: A total of 155 HIV-1-positive patients and 103 healthy HIV-negative control subjects of comparable age and sex ratio.

Intervention: None.

Main Outcome Measure: Clinical examination findings.

Results: Nail symptoms were present in 67.7% of HIV-

positive patients vs 34.0% of controls ($P < .001$). The following symptoms were significantly more frequent in the HIV group: clubbing (5.8%) ($P < .05$), transverse lines (7.1%) ($P < .01$), onychoschizia (7.1%) ($P < .05$), leukonychia (14.3%) ($P < .001$), and longitudinal melanonychia (14.8%) ($P < .01$). The main finding was onychomycosis in 30.3% of patients vs 12.6% of controls ($P < .001$). *Trichophyton rubrum* was present in 48% of onychomycoses and unusual *Candida* species were also recorded. Multiple fungi were frequently cultured in a single patient. The mean CD4⁺ cell count was lower in patients with onychomycosis and the frequency of onychomycosis increased in advanced stages of HIV disease. Acquired total leukonychia of the 20 nails was present in 4% of patients.

Conclusion: Nail symptoms are much more frequent in patients with HIV than in healthy controls, and some of them could be linked to the level of immunosuppression.

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From the Dermatology Department (Drs Cribier, Leiva Mena, and Grosshans), HIV Care Centre (Drs Rey, Partisani, and Lang), and Epidemiology Department of Dentistry School (Mr Fabien), University Hospital, Strasbourg, France.

HERE ARE many mucocutaneous changes or specific skin diseases associated with human immunodeficiency virus (HIV) infection.^{1,2} Only a few studies have given attention to the nail changes that can occur in association with HIV infection.³⁻⁶ It is now established that tinea pedis and onychomycosis are more frequent in HIV-infected patients,^{7,8} who can present with uncommon proximal or superficial onychomycosis.^{9,10} Another well-known ungual symptom is the presence of longitudinal melanonychia associated or not with treatment by zidovudine.¹¹⁻¹⁵ Rare cases of yellow nail syndrome were described in association with the acquired immunodeficiency syndrome (AIDS).¹⁶ Nevertheless, the specificity of nail symptoms observed in an HIV population was never assessed. Moreover, except for the data reported in

the study by Valenzano et al,³ the prevalence of nail changes in patients with HIV is not exactly known. The purpose of this prospective study was to evaluate the frequency of nail changes in 155 HIV-infected patients and the specificity of these findings by the comparison with 103 HIV-negative control subjects who were examined during the same period.

RESULTS

PATIENTS

The 155 HIV-positive patients included 38 women and 117 men with a mean age of 36.5 ± 8.0 years (range, 21-64 years). The mean duration of HIV infection (time between first positive HIV test result and nail study) was 6.7 ± 3.6 years (range, 6 months to 14.5 years). The mode of transmission was sexual in 122 patients (homosexu-

PATIENTS AND METHODS

One hundred fifty-five patients followed up at Centre d'Information et de Soins de l'Immunodéficience Humaine, Strasbourg, France, were examined during 1 of their regular checkups. All gave oral informed consent for clinical examination and photography of their 20 nails. All had proven HIV-1 infection, ie, 2 different positive enzyme-linked immunoabsorbent assays (ELISAs) and positive Western blot. Patients with psoriasis, eczema, or erythroderma were excluded from this study, because their nail symptoms were likely to be due to these dermatological conditions. The demographic data, the mode of transmission, the stage of disease, and the duration of known HIV infection were recorded. Total CD4⁺ cell count and HIV-1 plasma viral load (Amplicor HIV monitor, Roche Diagnostic Systems, Basel, Switzerland) were systematically investigated. Patients were examined between October 1996 and May 1997.

During the same period, 103 HIV-negative control subjects of comparable sex ratio and mean age were examined by the same investigator (M.L.M.). Most were members of the medical staff of Strasbourg University Hospital, Strasbourg, who were included on the basis of a negative HIV ELISA in the past 3 months. The other control subjects were healthy volunteer patients who consulted only for HIV testing.

For all patients, a standardized examination was performed in which the changes in surface, color, thickness, and curvature of nail plates were noted. Changes in periungual area were also recorded. In case onychomycosis was suspected, mycological culture was proposed to these patients. When the diagnosis of onychomycosis was made, the other abnormal findings on the same nail were not recorded, since discoloration and changes in consistence of the nail plate are mainly due to onychomycosis. For example, nails with onychomycosis were not included in the count of leukonychia.

The frequency of the various nail changes in the 2 groups was compared using the χ^2 test. The frequency of each symptom was also examined according to stage of disease (1993 Centers for Disease Control and Prevention [CDC] classification), mean CD4⁺ cell count, and viral RNA level. Results are reported as mean \pm SD.

als, 76; heterosexuals, 46), intravenous drug use in 21, transfusion or hemophilia in 6, and unknown in 6. The mean CD4⁺ cell count was $0.46 \pm 0.32 \times 10^9/L$ (range, $0.001\text{--}1.354 \times 10^9/L$). The CDC stage of HIV disease was stage A in 57 patients, stage B in 74, and stage C in 24. The results of HIV RNA levels were under the cutoff (199 copies per milliliter) in 46 patients, 200 to 999 copies per milliliter in 34 patients, 1000 to 9999 in 30 patients, 10 000 to 99 999 in 29 patients, and more than 100 000 in 16 patients. Many patients were also coinfecte

d with hepatitis B virus or hepatitis C virus (HCV): 69.7% had hepatitis B virus antibodies, but only 12.9% had circulating hepatitis B surface antigen, and 20% of patients had HCV antibodies. Only 1.85% of patients had both HCV

antibodies and hepatitis B surface antigen. Antiretroviral agents were administered in 143 patients (zidovudine alone in 2 patients, 2 drugs in 55 patients, 3 drugs in 82 patients, and 4 drugs in 4 patients). Thirty-three patients also had prophylactic therapy, 21 of them being treated with a combination of trimethoprim and sulfamethoxazole.

The HIV-negative control subjects included 22 women and 81 men. Their mean age was 36.4 ± 7.0 years.

NAIL CHANGES

Among the HIV-positive group, only 50 (32.3%) of 155 patients had normal findings on examination of their 20 nails (no significant change in color, curvature, thickness, or surface of the nail plate). The mean number of abnormal nails in the other 105 patients was 9.4 ± 6.1 . In the control group, 68 (66.0%) of 103 patients had no significant nail changes. The mean number of abnormal nails was 4.3 ± 3.2 in the 35 HIV-negative controls who had nail changes. Of the 86 HIV-positive patients who had nail changes other than onychomycosis, 34 were unemployed, and among the 52 patients who were still working at the time of this study, only 20 were exposed to mechanical trauma or chemicals during their working time. Frequent use of detergents or soaps was noted in 9 patients. We did not find more frequent nail changes or specific ungual symptoms in the subgroup of HIV-infected patients who had manual occupations.

The main changes affecting the nail plate and the periungual area are detailed in **Table 1**. A clinical diagnosis of onychomycosis was made in 47 patients (30.3%). Mycological cultures could be done in 42 patients (**Table 2**). Positive direct examination and mycological culture was noted in 27 patients (64% of patients with a clinical diagnosis of onychomycosis). The superficial form of onychomycosis (**Figure 1**) due to infection with *Trichophyton rubrum* was observed in only 2 patients, and proximal onychomycosis was also noted in only 2 patients. The other patients had total or distal-lateral onychomycosis. A clinical diagnosis of onychomycosis was made in only 12.6% of the 103 control subjects, which is much lower than in the HIV group ($P < .001$). Mycological cultures were performed in 10 of them, and were positive in 7 (70% of cultures). *Trichophyton rubrum* was isolated in 3 subjects (43% of positive cultures), *Candida* species in 2, *Scopulariopsis brevicaulis* in 1, and *Penicillium* species plus *Fusarium* species in 1.

One of the major findings was the high frequency of longitudinal melanonychia (**Figure 2**), present in 14.8% of HIV-positive patients. Among this group of 23 patients, 3 were African American and 1 was Indian, who had pigmented bands for years. The 19 remaining patients were white patients who did not notice these pigmentary changes before HIV infection, except in 1 case. We also observed proximal or total leukonychia (**Figure 3**) in 14.2% of patients vs 0% of controls. Six of the patients had their 20 nails affected by a total white homogeneous discoloration, without any other change of the nail plate. All these patients noted that this change occurred after the diagnosis of HIV infection. Powdery discolored or subungual hyperkeratosis was not present in these patients. Among abnormalities of the nail plate, clubbing, onychoschizia, and trans-

Table 1. Main Symptoms Observed in the 2 Groups*

Symptom	No. (%) Localization†		P
	HIV-Positive Group	HIV-Negative Group	
Curvature			
Clubbing	9 (5.8) h, 3; b, 6	0	.03
Koilonychia	4 (2.6) h, 1; f, 3	0	.22
Plicature	1 (0.6) f, 1	0	.86
Onychogryposis	1 (0.6) f, 1	0	.86
Surface			
Longitudinal ridging	18 (11.6) h, 17; b, 1	14 (13.6) h, 13; f, 1	.66
Transverse lines	12 (7.7) h, 11; b, 1	0	<.01
Pitting	5 (3.2) h, 5	2 (2) h, 2	.53
Onychoschizia	11 (7.1) h, 8; b, 3	2 (2) h, 2	<.05
Onychomadesis	1 (0.6) h, 1	0	.86
Pigmentary changes			
White nails	6 (3.9) b, 6	0	.11
Half-and-half nails	16 (10.3) h, 10; b, 6	0	<.001
Melanonychia	23 (14.8) h, 13; f, 3; b, 7	2 (2) h, 2	<.001
Longitudinal red bands	8 (5.2) h, 7; f, 1	0	.06
Yellow nails	0	2 (2) f, 2	.30
Brittle nails	8 (5.2) h, 6; f, 1; b, 1	0	.06
Splinter hemorrhages	10 (6.5) h, 8; b, 2	3 (2.9) h, 3	.20
Onychomycosis	47 (30.3) h, 3; f, 42; b, 2	13 (12.6) f, 13	<.001
Periungual area			
Periungual erythema	16 (10.3) h, 14; f, 0; b, 2	5 (4.9) h, 5	.08

*HIV indicates human immunodeficiency virus. Symptoms that were significantly more frequent in the HIV-positive group are in boldface type.

†Localization of nail changes: h indicates hands only; f, feet only; and b, both hands and feet.

Table 2. Results of Mycological Cultures in HIV-Positive Patients

Dermatophytes species (total)	12
<i>Trichophyton rubrum</i>	10
<i>Trichophyton mentagrophytes</i>	2
<i>Trichosporon cutaneum</i>	1
Candida species (total)	9
<i>Candida albicans</i>	2
<i>Candida parapsilosis</i>	3
<i>Candida tropicalis</i>	1
<i>Candida ciferrii</i>	1
<i>Candida famata</i>	1
<i>Candida guilliermondii</i>	1
Aspergillus species (total)	5
<i>Aspergillus ustus</i>	1
<i>Aspergillus candidus</i>	1
<i>Aspergillus niger</i>	1
<i>Aspergillus versicolor</i>	2
Scytalidium dimidiatum	1
Rhodotorula species	4
Penicillium species	5
Cladosporium species	2
Fusarium species	2
Botryotrichum piluliferum	1
Mold fungi	2
Positive mycological culture (total)	27
Negative culture	15

*HIV indicates human immunodeficiency virus.

verse lines were significantly more frequent in the HIV group. True clubbing was observed in 9 patients and significant increased transverse curvature without change in the proximal nail fold in 4 other patients. Brittle nails were observed only in the HIV group. It is interesting to note the frequency of the unusual transverse grooves (7.7%),



Figure 1. Superficial onychomycosis due to infection with *Trichophyton rubrum*.

or Beau lines, in the HIV group. Permanent periungual erythema was also frequently noted (Figure 3), even in patients with normal nail plates. This change affected most often the 10 fingernails or the 20 nails. In many patients a diffuse erythema of the distal phalangea without paronychia was noted, but none of them experienced Raynaud phenomenon.

The mean CD4⁺ cell count and the frequency of each group of symptoms according to stage of HIV disease are detailed in **Table 3**. The mean CD4⁺ cell count of pa-



Figure 2. Longitudinal melanonychia of 1 hand nail.



Figure 3. Proximal leukonychia with marked periumgual erythema.

Table 3. Frequency of Nail Symptoms (by Groups) According to CDC Stage of HIV Infection, and CD4+ Cell Count in Patients With and Without Nail Symptoms*

Nail Symptom	% of Patients			P	Mean \pm SD CD4+ Cell Count, $\times 10^9/L$		P
	Stage A	Stage B	Stage C		Symptom Present	Symptom Absent	
Curvature	7.5	10.5	41	<.02	0.39 \pm 0.30	0.46 \pm 0.32	.30
Surface	54	30	33	.28	0.49 \pm 0.29	0.44 \pm 0.32	.37
Pigmentary changes	28	39	29	<.50	0.39 \pm 0.23	0.49 \pm 0.35	<.04
Brittle nails	5	1	17	.08	0.37 \pm 0.14	0.46 \pm 0.32	.09
Onychomycosis	21	30	54	<.02	0.38 \pm 0.30	0.49 \pm 0.32	.03
Periumgual erythema	5	9.5	8.3	>.50	0.46 \pm 0.20	0.46 \pm 0.32	.99

*CDC indicates Centers for Disease Control and Prevention; HIV, human immunodeficiency virus.

tients with at least 1 nail symptom was $0.43 \pm 0.28 \times 10^9/L$ vs $0.51 \pm 0.37 \times 10^9/L$ ($P = .15$) in patients with normal nail examination. With regard to CDC stage of the disease, 61% of patients with stage A disease, 66% of those with stage B disease, and 83% of those with stage C disease had nail symptoms ($P = .06$). Onychomycosis was present in 21% of patients with stage A disease compared with 30% of patients with stage B and 54% of patients with stage C disease ($P < .02$). The mean CD4+ cell count in patients without onychomycosis was significantly higher than in patients with onychomycosis ($P = .03$).

We found no significant differences in the frequency of nail symptoms according to viral load.

COMMENT

In this prospective study of 155 HIV-infected patients, we found a 67.7% prevalence of nail changes (vs 34% in healthy controls), which is higher than the prevalence rate of 32.5% found in the study by Valenzano et al.³ Since the frequency of pathological nails increases with time, it is important to compare the nail changes with those of age-matched controls. Nevertheless, our study cannot confirm that the findings are specifically due to HIV infection. A comparison with patients with other chronic illnesses could help to distinguish which nail symptoms are more specifically associated with HIV.

Our work confirms that onychomycosis affects one third of HIV-infected patients. The frequency of onychomycosis in our control group was similar to the 13.7% prevalence published in Ohio.¹⁷ We have found only a minority

of cases of superficial onychomycosis,⁸ but unusual *Candida* species were cultured in the HIV group, such as *Candida gulliermondi* or *Candida ciferii*. Most HIV-positive patients had onychomycosis due to infection with *T rubrum*, and coinfection with mold fungi or with *Candida* was extremely frequent. Our results suggest that onychomycosis is related to the degree of immunosuppression. Korting et al¹⁸ have noted a higher frequency of onychomycosis in terminal stage of HIV infection, as have Daniel et al.⁴ Onychomycosis can be observed in the early stages of HIV infection, but involvement of 10 or 20 nails (5 patients in our group) is more common in advanced stages.¹⁹ Although the antimicrobial susceptibility seems to be normal,¹⁸ onychomycosis in HIV-infected patients is more difficult to treat.²⁰ This could be because of the frequent coinfection by molds or the presence of unusual pathogens.

Most nail symptoms recorded in the present study have been previously described in HIV-positive patients: longitudinal melanonychia,¹²⁻¹⁴ splinter hemorrhages,²¹ transverse and longitudinal ridging,²² and clubbing.²³ Recently, the importance of digital clubbing in children with AIDS was emphasized by Graham et al,²⁴ but this sign is probably not extremely frequent.²⁵ None of our 9 patients with true clubbing had pulmonary disease and only 3 of them were smokers. Since curvature changes (mainly clubbing) seemed to be related to the level of immunosuppression, our data reinforce the suggestion of Graham et al, who claimed that clubbing could be of importance for the definition of pediatric AIDS.²⁴

Transverse grooves or transverse ridging across the nail have been rarely described in HIV-positive patients⁵ and are

supposedly a consequence of episodes of severe illness or of serum zinc depletion. In our 12 patients with this sign, frequent computer keyboard use was noted in only 3 patients. No other mechanical factor could be demonstrated. Onychoschizia is also considered to be of external origin.²⁶ Occupational factors were not evidenced in HIV-infected patients with onychoschizia: 6 of 11 were unemployed and had no sign of physical trauma of the hands and only 3 were manual workers. The mean age of these 11 patients was only 33 years, and none had sign of premature aging. To our knowledge, onychoschizia has not been associated with AIDS until now. It can be hypothesized that discoloration, brittle nails, and onychoschizia reflect the various conditions observed in patients with HIV, but we are not able to affirm that they are consecutive to metabolic changes, repeated infectious diseases, or nutritional problems. The role of external factors is probably only accessory in this study, since patients having a manual profession, especially those who frequently used detergents, had no more nail changes than the other patients of the group.

We have observed 6 cases of acquired leukonychia of the 20 nails, which to our knowledge has not been previously described. True leukonychia is extremely rare and is not recorded in HIV disease,²⁶ except in 1 reported case.²² Proximal or subtotal leukonychia was present in more than 10% of our HIV-infected patients. Some of them had typical Terry nails,²⁶ but none had cirrhosis, and results of liver tests were within normal range. Half and half nails were observed in some of our patients without significant renal changes. The group of patients with proximal or total leukonychia was characterized by lower CD4⁺ cell count ($0.29 \pm 0.20 \times 10^9/L$ vs $0.48 \pm 0.32 \times 10^9/L$; $P < .001$). The occurrence of longitudinal melanonychia in HIV-positive patients is now well established. It has been attributed to the use of zidovudine, but it also has been described in patients who were not receiving antiretroviral treatments.¹⁵ This symptom could be due to increased levels of α -melanocyte-stimulating hormone.^{15,22} In our 18 white patients with acquired melanonychia, zidovudine was or has been administered in all cases, in combination with other antiretroviral drugs in 16 cases. Remarkably, the known duration of HIV infection was higher than 8 years in 12 of the 18 patients (range, 8–12 years), suggesting that long exposure to antiretroviral drugs could be a causal factor in melanonychia. The role of other drugs in the nail changes observed in this study is impossible to demonstrate, since we could not find differences in treatment regimens of patients with or without nail symptoms. Among patients who were treated with trimethoprim-sulfamethoxazole, 11 had no nail changes, 2 had longitudinal ridging, and 4 had leukonychia. The only specific finding that could be attributed to this drug was onychomadesis as a sequela of toxic epidermal necrolysis.

Periungual erythema with or without changes in the nail plate was frequently observed in our patients. "Red fingers" have been described in patients coinfected by HCV and HIV.²⁷ In the present study, the frequency of this symptom was not significantly higher than in the control subjects, and was present in only 2 patients coinfected by HCV. This sign was not linked to any of the HIV data analyzed. It is likely that red fingers are not specific of either HIV or HCV infection. We noted that peri-

ungual erythema in HIV-positive patients was much more intense than in the control group.

In conclusion, systematic nail examination of HIV-infected patients is valuable, because of frequent onychomycosis and various changes of the nail plate, mainly leukonychia and melanonychia, that can be related to the severity of immunosuppression. The cause of these findings requires further studies.

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Reprints: Bernard Cribier, MD, PhD, Clinique Dermatologique, CHU 1 Place de l'Hôpital, 67091 Strasbourg Cedex, France.

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