CLINICAL REPORT

Clinical Analysis of Skin Lesions in 796 Chinese HIV-positive Patients

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Skin lesions are often associated with human immunodeficiency virus (HIV) infection, reflecting the immunocompromised status of the individual. We investigated the relationship between skin lesions and immune function in a retrospective study of 796 Chinese HIV patients with and without highly active antiretroviral therapy (HAART). Of the 651 patients who had not received HAART, we found that 531 (81.6%) had apparent skin lesions. The incidence of infectious skin diseases (fungi, viruses, bacteria, spirochetes and parasites) and non-infectious skin diseases (excluding skin cancer) was 68.8% and 34.9%, respectively. Mean $CD4^+$ T-cell counts and $CD4^+/CD8^+$ ratios were lower in patients with skin lesions than in patients without lesions ($178 \pm 96/\mu l$ vs. $306 \pm 189/\mu l$ ($p < 0.05$) and 0.22 vs. 0.34 ($p < 0.01$), respectively). Candidiasis (25.8%), eczema (19.2%), nodular prurigo (13.8%), dermatophyte infections (10.6%) and herpes zoster (9.4%) were most common in Chinese patients with HIV. Among the 145 patients who had started HAART, there was a significantly lower prevalence of skin diseases (29.0%), although drug eruptions (12.4%) were more commonly observed. These findings indicate that HAART often reduces the incidence of infectious and non-infectious skin lesions in patients with HIV, but can itself be the cause of drug eruptions. *Key words: HIV infection; skin mucosal manifestation; $CD4^+$ T-cell count.*

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Skin and mucocutaneous diseases can be seen in every stage of human immunodeficiency virus (HIV) infection, including asymptomatic stages (1). Previous studies have found that approximately 90% of HIV-infected patients have skin lesions (2, 3) and that these are often the first indication that the patient is infected with HIV. The mechanism by which HIV-infected patients are prone to skin disease appears to be correlated with the degree of immunodeficiency (4). Many skin diseases may in fact be considered valuable and sensitive indicators for the diagnosis of HIV and for monitoring disease progression and treatment efficacy (5, 6). Before the development of highly active antiretroviral therapies (HAART), HIV-related skin diseases were common in Chinese patients (7). Following the introduction of HAART, the occurrence of mucocutaneous diseases has been reduced. A decreased incidence of many skin lesions is thought to result from immune reconstitution, while persistence of skin disease is thought to be due to a failure of antiviral treatment as reflected in a reduced $CD4^+$ T-cell count and increased viral load (8).

Since the diagnosis of skin disease is relatively intuitive, monitoring skin lesions has practical applications; some studies have shown that candidiasis, oral hairy leukoplakia or seborrhoeic dermatitis may be strong indicators of underlying HIV infection (9–11). However, few reports (7, 8) have investigated the prevalence of skin lesions among HIV-infected patients in China. We have conducted a retrospective analysis of skin diseases among HIV/acquired immune deficiency syndrome (AIDS) patients who first presented to Beijing Youan Hospital Outpatient Services Department or were admitted to the hospital between May 2001 and May 2007. The incidences of various skin and mucocutaneous diseases were assessed to determine the relationship between the presence of mucocutaneous lesions, immune function and disease development in AIDS patients, and to determine the effects of HAART on occurrence of mucocutaneous diseases among HIV-infected patients.

MATERIALS AND METHODS

Clinical data

Clinical records were obtained for patients who first presented to Beijing Youan Hospital Outpatient Services Department or were admitted to hospital and confirmed as having HIV or AIDS between May 2001 and May 2007. A total of 796 cases, including 164 outpatient cases and 632 inpatient cases, were obtained and examined for the current study. This research received approval and accreditation from the hospital medical ethics committee.

To confirm HIV seropositivity, an enzyme-linked immunosorbent assay was used for the first screening (Organon Teknika Corporation, Molestraat, The Netherlands) followed by Western immunoblotting. The diagnosis of AIDS was based on the standards set by United States Centers for Disease Control and Prevention. FACScalibur flow cytometry with BD TriTEST™ three-color reagent (BD Biosciences, Shanghai, China), was used to evaluate $CD4^+$ T-cell count and $CD4^+/CD8^+$ ratio in all patients. The antiviral medication given to most patients was the front-line medicine provided free of charge by the government health services in China. Antiretroviral combinations included azidothymidine or stavudine + lamivudine or dideoxyinosine +

efavirenz or nevirapine. In 4 cases, it was necessary to change the drug combination to Kaletra (lopinavir and ritonavir) or indinavir due to treatment failure or adverse side-effects. We observed the prevalence of various skin diseases among HIV-infected patients, the characteristic clinical manifestations before intervention with HAART and examined the correlation between disease manifestation, the number of skin lesions, and CD4 T-cell count. We also studied the occurrence of skin diseases among patients who received HAART and asked patients about any change in their skin diseases after the commencement of HAART. Because the data on 145 HAART-treated individuals before treatment were incomplete, in order to see the effect of HAART on the skin symptoms we compared the incidence of skin disease between patients with and without HAART. Based on the mucocutaneous manifestations (including mucocutaneous diseases clearly diagnosed by clinical or laboratory studies during the previous 3 months), a detailed enquiry into the medical history and health of patients and clinical diagnoses was performed. Some cases required further diagnostic testing by fungal culture or skin biopsy.

Statistical analysis

We used SPSS (ver. 11.0) (SPSS Inc., Chicago, IL, USA) for all statistical analyses. The independent sample *t*-test was used to determine significant differences between data sets and considered $p < 0.05$ to be statistically significant.

RESULTS

Demographic data

Among 796 cases of HIV-positive/AIDS patients, 505 cases were male (63.4%) and 291 cases were female (36.6%). Most patients were aged between 20 and 50 years with a mean age of 36 ± 11.9 years at presentation. There were 706 patients diagnosed with AIDS at their first presentation. A total of 470 cases had acquired HIV through blood or plasma transfusion (mostly from Henan, Hebei and Shanxi provinces in China), 305 cases were acquired by sexual transmission (of which 180 cases were homosexual transmission), 16 cases were acquired through intravenous drug use, and 5 cases were due to mother-to-child transmission.

Disease spectrum of skin diseases among HIV-infected/AIDS patients before HAART

Of 651 patients who did not receive HAART, 531 cases (81.6%) had at least one skin disease. Most of these patients also had opportunistic infections. Some clinical examples of the mucocutaneous disease are shown in Fig. 1. The distribution of diseases is shown in Table I. The most common mucocutaneous diseases were oral candidiasis (25.8%), eczema (19.2%), nodular prurigo (13.8%), dermatophyte infection (10.6%), herpes zoster (9.4%), oral hairy leukoplakia (6.5%), syphilis (5.5%), and condylomata acuminate (3.1%). Grouped together, infectious diseases (caused by fungi, viruses, bacteria, spirochetes or parasites) accounted for 68.8% and non-infectious skin diseases (excluding skin cancer) for 34.9% of the mucocutaneous manifestations in patients without HAART.

Correlations between skin lesions and immune function in HIV-infected patients before HAART

The incidence of skin lesions among the patients were categorized by CD4+ T-cell count. At < 50 cells/μl 97.7% (127/130) of the patients had skin lesions,

Fig. 1. Complications of HIV infection with (A) *Penicillium marneffei* secondary infection, (B) herpes zoster infection, (C) oral hairy leukoplakia, and (D) nodular prurigo.

Table I. *Clinical analyses of HIV-positive patients with various mucocutaneous manifestations*

Mucocutaneous manifestations, n (%)	Without HAART (n=651)	With HAART (n=145)	Mean CD4+(/µl)	Mean CD4+/CD8+ ratio	CD4+<200/µl and/or complicated opportunistic infections
Viral infection	149 (22.9)	11 (7.6)			
Herpes zoster	61 (9.4)	6 (4.1)	152	0.17	32 (48)
Oral hairy leukoplakia	42 (6.5)	0	68	0.12	42 (100)
Molluscum contagiosum	14 (2.2)	0	185	0.19	7 (50)
Herpes simplex	12 (1.8)	2 (1.4)	341	0.39	5 (36)
Condylomata acuminata	20 (3.1)	3 (2.1)	269	0.30	6 (26)
Bacterial infection	17 (2.6)	2 (1.4)	213.8	0.24	8 (42)
Fungus infection	242 (37.2)	5 (3.5)			
Dermatophytosis	69 (10.6)	5 (3.5)	138	0.18	52 (70)
Oral candidiasis	168 (25.8)	0	101	0.17	151 (90)
Penicillium marneffei	5 (0.8)	0	7	0.01	5 (100)
Treponema pallidum	36 (5.5)	4 (2.8)	375	0.38	9 (23)
Scabies	4 (0.6)	0	74	0.18	4 (100)
Non-infectious diseases	227 (34.9)	34 (23.5)			
Eczema	125 (19.2)	11 (7.6)	63	0.15	124 (90)
Nodular prurigo	90 (13.8)	5 (3.5)	97	0.21	88 (93)
Drug eruption	7 (1.1)	18 (12.4)	58	0.16	21 (84)
Psoriasis	3 (0.5)	0	335	0.35	3 (100)
Seborrhoeic dermatitis	2 (0.3)	0	108	0.20	2 (100)
Tumour	7 (1.1)				
Kaposi's sarcoma	2 (0.3)	0	18	0.06	2 (100)
Lymphoma	4 (0.6)	0	14	0.06	4 (100)
Squamous cell carcinoma	1 (0.2)	0	13	0.04	1 (100)

at 50–199/µl 90.4% (206/228) had skin lesions, and at a T-cell count of ≥200/µl 54.8% (240/438) had skin lesions. The average CD4+ cell count in the group of patients with skin diseases was 178 cells/µl and the average CD4+/CD8+ ratio was 0.22. The average CD4+ cell count was significantly higher in the group of patients without skin disease (305/µl; ($p<0.01$)) who also had a higher CD4+/CD8+ ratio (0.34; ($p<0.01$)). Additionally, we observed patients with a CD4+ cell count of <200/µl who were prone to candidiasis (25.81%), dermatophytosis (10.60%), herpes zoster (9.37%), and molluscum contagiosum (2.15%). In contrast, patients with a CD4+ cell count of <100/µl were prone to eczema, nodular prurigo, oral hairy leukoplakia, and disseminated *Penicillium marneffei* infection.

Correlation between the number of types of skin diseases and immune status in AIDS before HAART

Out of a total of 401 AIDS patients, 201 (50.4%) had only one type of skin lesion, 143 patients (18.0%) had two different types of lesions, while 29 patients (3.6%) had three or more different types. The mean CD4+ cell counts in patients with one, two and three or more skin lesions were 212±61/µl, 137±31/µl and 50±16/µl, respectively, and the average CD4+/CD8+ ratios were 0.26, 0.14, 0.07, respectively. The correlation coefficient was −0.336 ($p<0.01$), indicating that the more types of skin lesions observed in an HIV-positive patient the higher is the probability of a reduced immune capacity. In particular, a patient who has two or more skin diseases indicated progression to AIDS.

Variation in the incidence and disease spectrum of skin diseases after HAART

Following an initial diagnosis, we gave 145 patients antiretroviral therapy (HAART) and treatment for opportunistic infections (see Materials and Methods). The median duration of follow-up of patients on HAART included in this study was 5.6 (interquartile range (IQR), 1.9–8.3) months; patients were to continue HAART after the last follow-up. Among patients treated with HAART, we observed 29% (42/145) who had at least one type of mucocutaneous manifestations within 8.3 months after the commencement of HAART (Table I). These cases had a mean CD4+ cell count of 57±18/µl at baseline. Drug eruptions were the most common side-effect and were reported in 18 cases (12.4%), of which 15 were caused by non-nucleoside reverse transcriptase inhibitors or protease inhibitors, and 3 were caused by sulphonamide drugs. In contrast, all other types of mucocutaneous manifestations were less frequent in this group of patients. For instance, the incidence of eczema was significantly decreased (7.6%) in patients who underwent HAART compared with 19.2% in those without HAART and the frequency of dermatophyte infection (3.5%) was only one-third of that in the control group (see Table I). There was no candidiasis, *Penicillium marneffei* infection or oral hairy leukoplakia observed in these patients.

Herpes zoster and molluscum contagiosum appeared to be less common in the HAART group. No significant difference was seen in the incidence of herpes simplex and condylomata acuminate in HAART patients; but since we did not record the HAART-treated patients' skin status before treatment we cannot disregard the probability that the two groups of patients (with and without HAART) showed a different prevalence of mucocutaneous manifestations to begin with.

DISCUSSION

Decreased immune function in the skin is correlated with many HIV-related non-infectious skin diseases (12). The T-helper cells are seriously impacted by HIV infection, whereby the normal Th_1-mediated immune response is converted to a Th_2-mediated response resulting in severe skin disease (13). As HIV infection progresses, skin diseases gradually become more aggressive and widespread throughout the body, with a higher rate of recurrence and refractory disease (14). Therefore, HIV/AIDS-related skin lesions are often important indicators for the clinician as to the presence of HIV infection and the development of AIDS.

Previous studies show that dermatological manifestations are seen at every stage of HIV/AIDS and are often the presenting feature (1). These manifestations not only act as disease markers, but also reflect the underlying immune status (14). Osborne et al. (12) previously found that patients with lower $CD4^+$ cell counts were prone to infectious skin diseases. Additionally, Uthayakumar et al. (15) also showed that the incidence of skin diseases associated with HIV infection in Brighton was 91.4% and infectious diseases had the highest incidence among the patients. Our findings agree with these and other reports. Prior to the administration of HAART, oral candidiasis showed the highest incidence (25.8%) among the patients included in this study. However, we also observed eczema and nodular prurigo at a higher incidence among these patients, particularly in those with a history of blood transfusion or plasma donation. Research in Uganda (16) found that the incidence of eczema and nodular prurigo among HIV-infected patients was closely correlated with being bitten by arthropods. A study in Zimbabwean adolescents (17) also reported the most common HIV-related conditions to be pruritic papular eruptions (42%). Similar to these studies in developing countries, most of our patients came from Henan and Shanxi provinces (470 of 796) where health and economic conditions are poor, and we found a high incidence of pruritic eczema and nodular prurigo among these patients.

The incidence of various skin diseases in HIV/AIDS populations could be related not only to geographic location and economic conditions, but also ethnicity. For example, the incidence of seborrhoeic dermatitis in HIV-positive patients ranges from 30% to 83%, and is much higher in some areas than others (15). Seborrhoeic dermatitis occurs early in the course of HIV disease and may be an early clinical marker for HIV infection (11). In a cohort of 1,161 Spanish patients infected with HIV-1 for 3 years (mean CD4 count, 353/µl), oral candidiasis and seborrhoeic dermatitis were the most common mucocutaneous disorders (4). A clinical study from Asia showed the most common skin disorder in Singapore was pruritic papular eruption in patients with HIV infection, followed by psoriasis, seborrhoeic dermatitis, xerosis, herpes simplex and drug eruptions (18). However, our study found that the incidence of seborrhoeic dermatitis among AIDS patients in mainland of China is very low (< 1%).

Some infectious mucocutaneous diseases, such as oral hairy leukoplakia and *P. marneffei* infection, were seen in patients with severe immunosuppression ($CD4^+$ count, < 100/µl). Disseminated *P. marneffei* was highly localized to patients coming from Guangdong, Guangxi and Yunnan provinces. In these provinces of southern China it is currently considered that *P. marneffei* infection are related to local wild bamboo rat. We observed that 5 inpatients with disseminated *P. marneffei* infections also had other skin lesions, probably associated with the average $CD4^+$ cell count in these patients being only 7/µl.

Herpes zoster was observed in patients at all stages of HIV infection with frequent recurrence of lesions and post-herpetic neuralgia. The extent and severity of recurrence was correlated with immune status where patients with clinical AIDS sometimes had disease in bilateral peripheral nerves.

Eczema and nodular prurigo were the most common non-infectious diseases observed in the current study. Patients with these conditions were resistant to traditional treatment and were prone to repeated attacks (data not shown). HAART, however, effectively improved the skin lesions within 1–2 months of commencement. Patients with HAART who had persisting severe itching papules or nodules often showed antiviral treatment failure. Monitoring these symptoms could be used as a clinical marker to predict the virological outcome in resource-limited settings where CD4 count and viral load testing are unavailable.

The introduction of HAART substantially reduced mortality and opportunistic infection caused by HIV infection and effectively reduced the incidence of skin disease (19–21). The occurrence of both infectious and non-infectious skin diseases was substantially reduced in our patients on HAART. However, with the application of HAART, a series of new complications, such as drug eruption, emerged that should not be neglected. According to previous reports (21), HIV-infected patients have a higher incidence of adverse drug reactions than non-HIV patients. In the current study, we observed 18 cases of drug eruptions after receiving HAART and

anti-opportunistic infection treatment. It is noteworthy that within the first few months of receiving HAART, eczema, nodular prurigo, herpes zoster and other viral skin disease may occur, probably due to immune reconstitution inflammation syndrome (IRIS) caused by the late initiation of antiviral treatment (22–24). Eczema, nodular prurigo and herpes zoster were the main forms of dermatological condition observed in this study; however, other studies showed the most common dermatological IRIS is viral skin disease (25).

Here, we have presented the results of a large-scale clinical analysis of the types and distribution of skin disease in Chinese patients with HIV/AIDS with and without HAART. Our findings are similar to those from studies conducted in other populations where the variety, frequency and clinical manifestations of the skin diseases observed were closely correlated with the immune deficiency caused by HIV infection. However, due to geographical, environmental and racial differences, the incidences of different types of skin disease varied. Nevertheless, in regions with limited resources, the occurrence of skin diseases may be useful as a clinical indicator of HIV infection and for assessing the need for early antiviral intervention.

ACKNOWLEDGEMENTS

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