

Preliminary Study of Nine AIDS-Associated Skin Complications

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ABSTRACT

HIV related skin disease is one important case of HIV-associated complications, cause poor quality of life and even to mortality. In order to understand features of AIDS-associated skin complications in clinical. Blood items, microbe characterization and pathology of 9 patients derived from Nanyang Medical College hospitals with AIDS-associated skin diseases were measured by corresponding techniques. Of the 9 cases infected by different virus, fungus and bacteria showed different features of body surface and pathology. AIDS-associated skin complications show various clinical characterizations, combination different fields contribute to elucidate features of AIDS-associated skin complications.

Keywords: AIDS, AIDS-associated skin complications, Pathology

INTRODUCTION

In the world, patients of human immunodeficiency virus (HIV) infections have been reached to 35 million (31.8 million adults and 3.2 million children <15 years) globally [1]. Meanwhile, those of new HIV infections are gradually increasing in every countries, among of them, large of peoples are died in every year [1]. The major causes of mortality are derived from Acquired Immunodeficiency Syndrome (AIDS) related mortality as well as from opportunistic infections such as tuberculosis (TB) and cryptococcal infections. HIV related skin disease is one important case of HIV-associated complications, cause poor quality of life and even to mortality. It was estimated that up to 90% of HIV-infected individuals have associated skin and mucosal complications during the course of their illness [3]. Noteworthy, skin manifestations may be the potential signal of HIV infection and therefore present an opportunity for HIV testing and earlier diagnosis [3]. Some mucocutaneous conditions in particular are a proxy indicator for more advanced immunodeficiency and the need for prompt initiation of antiretroviral therapy [4,5]. Certain skin conditions can also lead to severe morbidity such as pain on swallowing from oropharyngeal candidiasis and recurrent infections that are difficult to treat, such as scabies [6,7]. Other conditions such as zoster and extensive tinea that are difficult to conceal may cause stigma and cause psychosocial stress and depression [8].

As to AIDS patients, HIV-associated skin complications shows a numbers of complex characterizations with respect of occurrence of novel pathogens. Therefore, it brings about great challenge for clinical treatment. Combination of different ways is an important to further elucidate characterizations and under mechanisms of HIV-related complication. Take into consideration extensive emergence of skin diseases of AIDS patients, in the current study, 9 cases of HIV-related skin diseases are analyzed by pathology, microbiology and image.

MATERIALS AND METHODS

Patient selection

The study was approved by Ethical Review Committee of Nanyang Medical University. Available participants were approached and informed of the study objectives, procedure and confidentiality issues by study coordinator. Patients who decided to participate in this study and provided written

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informed consent were asked to complete a survey to assess presence of HIV/AIDS-related symptoms.

Study design

Quantity of CD4⁺ T cell was measured using flow cytometry instrument (BD, USA) according to kit instructions. Histological analysis was performed by HE staining. Morphological observations of pathogens were fulfilled by microbe culture. Results of X-ray and computed tomography (CT) were used in imaging analysis, respectively.

RESULTS AND DISCUSSION

HIV-associated skin folliculitis eosinophilia

Case 1, a male had 34 years and was definitely diagnosed as AID by CDC. Quantity of CD4⁺ T cell was 9 μ l. Erythema and papules accompanied itching were found in face, neck, arms and legs. Invasived erythema and papules, fusion of partial papules without ulceration, erosion, scaling rash, desquamation were observed in neck, trunk and limbs (Figures 1A and 1B). Pathological results showed a large number of eosinophil infiltration were occurred in the dermal layer (Figures 1C and 1D). The patient was in the acute phase of HIV-associated skin folliculitis eosinophilia.

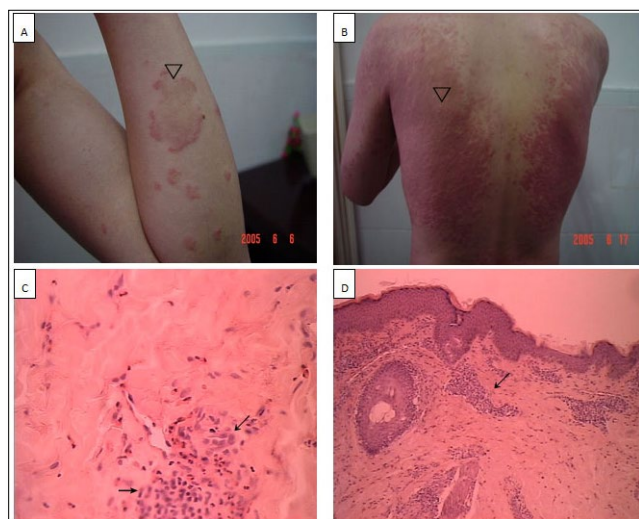


Figure 1. HIV-associated folliculitis eosinophilia. **A:** Skin rash of forearm; **B:** Skin rash of back; **C, D:** Results of skin HE staining.

▽: skin rash, →: eosinophil

HIV-associated skin complication of *Staphylococcus aureus* infection

Case 2, a female, 39 years, was definitely diagnosed as AID by CDC. Quantity of CD4⁺ T cell was 13 μ l. Multiple round ulcers formed pink granulation tissue on the surface were observed in lower segments of left and right legs by stereology examination (Figures 2A and 2B). Local tissues showed an obvious complication characterized by ulceration

and erosion of skin mucus, inflammatory leaching of surface, necrosis of epidermides and submucosal granulation tissue and scar formation (Figure 2B). Sebaceous glands and sweat gland showed normal appearances, but inflammatory infiltration could be found in the stroma of neutrophils, eosinophils and lymphocyte (Figures 2C and 2D). The patient was in the acute phase of HIV-associated skin infection of *S. aureus*.

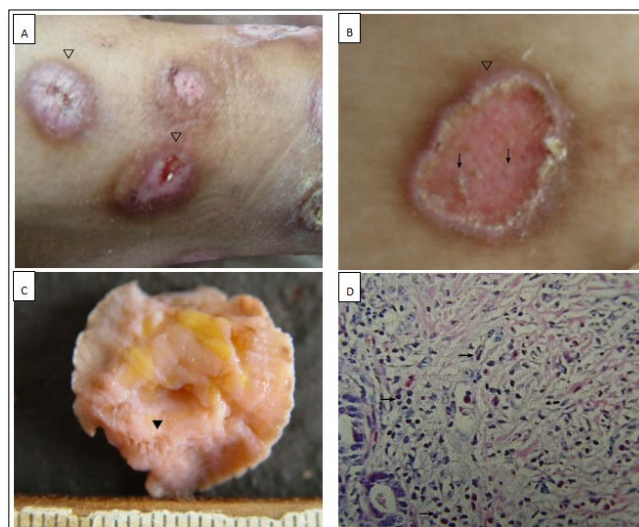


Figure 2. HIV-associated skin complication of *Staphylococcus aureus* infection. **A, B:** Ulcer of the lower limbs; **C:** Ulcer tissues; **D:** Result of skin HE staining.

▽: ulcer, ↓: bud tissue, →: infiltration cells

HIV-associated skin superficial complication of fungal infection

Case 3, a female, 32 years, was definitely diagnosed as AID by CDC. Quantity of CD4⁺ T cell was 98 μ l. Body temperature sustain at 38.9°C. Diverse symptoms including inflation of superficial lymph nodes, multiple-sites skin ulcers, membrane formed by white deposition in the tonsils of mouth were observed. Multiple ulcers with dark red color and epithelium drop of ulcerated tissue were widely observed (Figures 3A and 3B). Lymph node of biopsy showed fungal infection in which the mild spreading mycelium of yeast was detected (Figures 3C and 3D). Patient was in the period of remission of HIV-associated skin complication of candida infection.

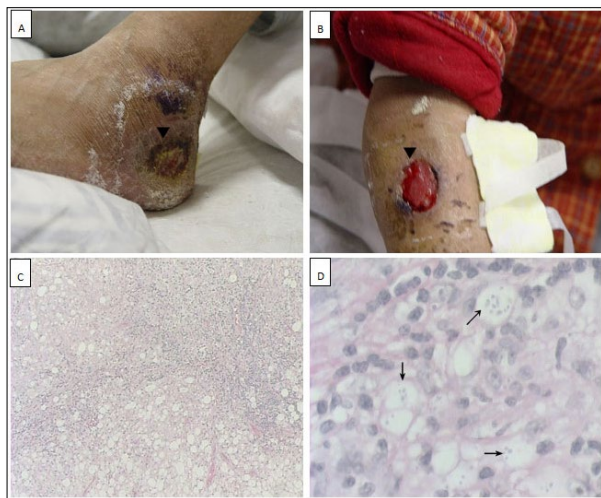


Figure 3. HIV-associated skin complication of candida infection. **A:** Skin ulcer of ankle skin; **B:** Skin ulcer of forearm; **C, D:** Lymph node tissue.

Case 4, a female, 42 years, was definitely diagnosed as AID by CDC. Quantity of CD4+ T cell was 28 μ l. Mild granulation tissue appeared in the surface of skin was observed by stereology check (**Figure 4A**). Local keratinization or hyperkeratosis of epithelium, enlarged keratinization of skin surface, thickened epithelium was observed by tissue biopsy (**Figure 4B**). In the dermis, some vacuolar degeneration, scattered infiltration of lymphocytes, some squamous epithelium with a mild to moderate atypical hyperplasia were found, although integrital hair roots and survived sebaceous were observed (**Figures 4C and 4D**). Patient was the acute phase of HIV-associated skin superficial infection of fungus.

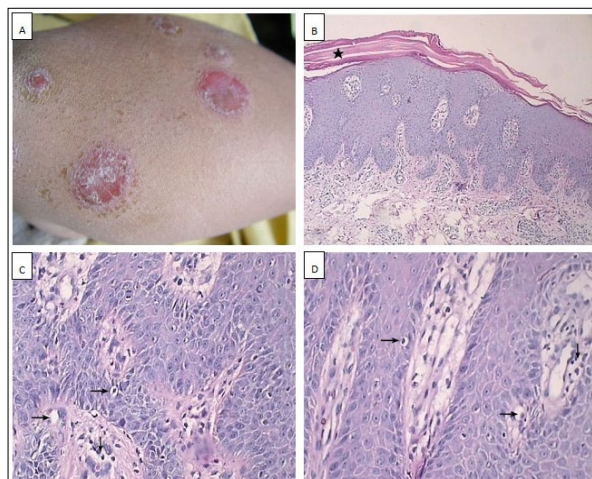


Figure 4. HIV-associated skin complication of fungus infection. **A:** Skin lesions of right upper arm; **B-D:** Results of skin HE staining.

★: tissue of keratinization, →: vacuolar cells, ↓: inflammatory cells

HIV-associated skin complication of cryptococcosis infection

Case 5, a female, 30 years, was definitely diagnosed as AID by CDC. Quantity of CD4+ T cell count was 28 μ l. Multiple furuncles and partial ulcer were found on the face (**Figures 5A and 5B**). Cryptococcus was isolated from the medium by microbial culture (**Figures 5C and 5D**). The patient was the acute phase of HIV-associated skin complication of cryptococcosis infection.

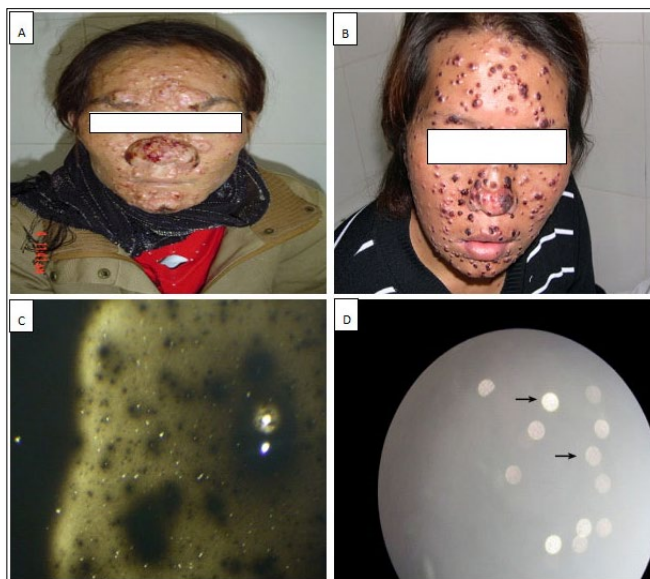


Figure 5. HIV-associated skin complication of cryptococcosis infection. **A, B:** Lesions of face; **C, D:** Results of microbe culture.

→: colony of cryptococcosis

HIV-associated skin complication of *Penicilliosis marneffei* infection

Case 6, a female, 31 years, was definitely diagnosed as AID by CDC and showed fever at 38~39°C, fatigue, poor appetite, maransis, weight loss, cough, white phlegm and sore throat. Quantity of CD4+ T cell was 150 μ l. Multiple complications were detected. In addition, red and dark red pimples were scattered in skin of all body at a diameter from 3 to 8 mm and caved ones were mainly occurred in the head face and trunk. Several white plaques could be observed in the mouth (**Figures 6A and 6B**). Pathological tissue biopsy showed an obvious fibrosis was found in lesion tissue (**Figure 6C**). Under high power microscopic view, mycelium of *P. marneffei* was detected in medium of microbiological culture (**Figure 6D**). The patient was the period of remission of HIV-associated skin complication of *P. marneffei* infection.

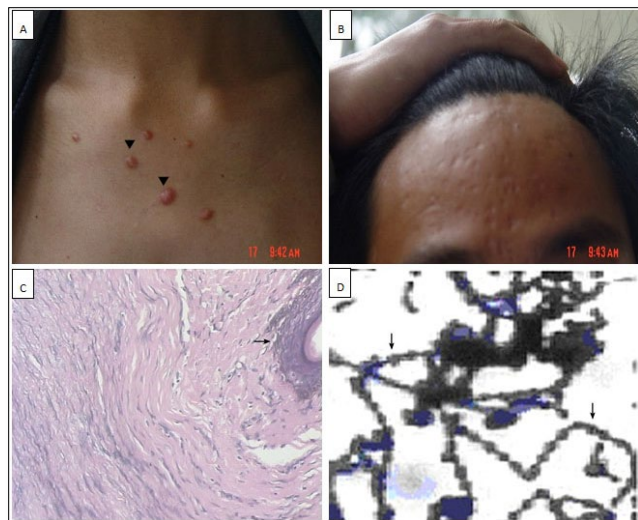


Figure 6. HIV-associated skin complication of *Penicilliosis marneffei* infection. **A:** Skin lesions of chest; **B:** Skin lesions of forehead; **C:** Results of skin nodules HE staining; **D:** Results of microbe culture.

→: tissue of fibrosis, ↓: mycelium of *Penicilliosis marneffei*

HIV-associated skin complication of herpes simplex virus infection

Case 7, a boy, 5 years, was definitely diagnosed as AID by CDC. Quantity of CD4+ T cell was 102 μ l. Fresh water vacuole was fund in hand back and feet, some ones were ulcerated and fused (**Figures 7A and 7B**). HE staining results showed that particles of inclusion virus were presented in lymphocytes and monocytes (**Figures 7C and 7D**). Patients was in the period of remission of HIV-associated skin complication of herpes simplex virus infection.

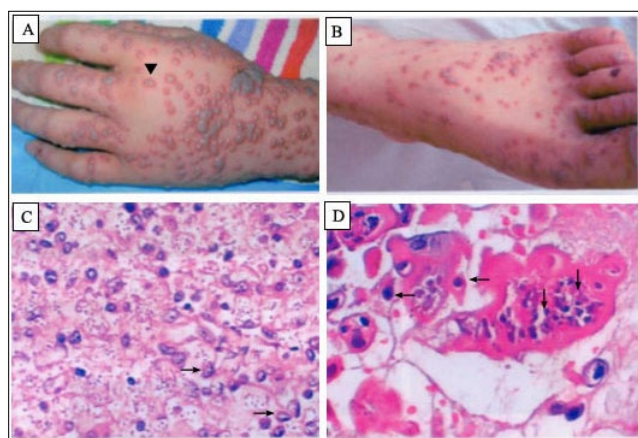


Figure 7. HIV-associated skin complication of herpes simplex virus infection. **A:** Lesions of hand back; **B:** Lesions of hand back of foot; **C, D:** Results of HE staining.

HIV-associated skin complication of herpes zoster virus infection

Case 1, a male, 42 years, was definitely diagnosed as AID by CDC and showed intermittent fever and limb weakness. Quantity of CD4+ T cell was 25 μ l. Zoster virus was observed in low part of xiphoid as well as face (**Figures 8A and 8B**). Growth of pathogenic microbes was observed by serum culture (**Figure 8C**). Intermittent fever and cough were repeatedly occurred in the night. In advanced stage of AID, multiple infections and diffuse high-density shadow in middle and lower regions of right and left lungs were fund in patient (**Figure 8D**). Patients was in the acute phase of HIV-associated skin complication of herpes zoster virus infection.

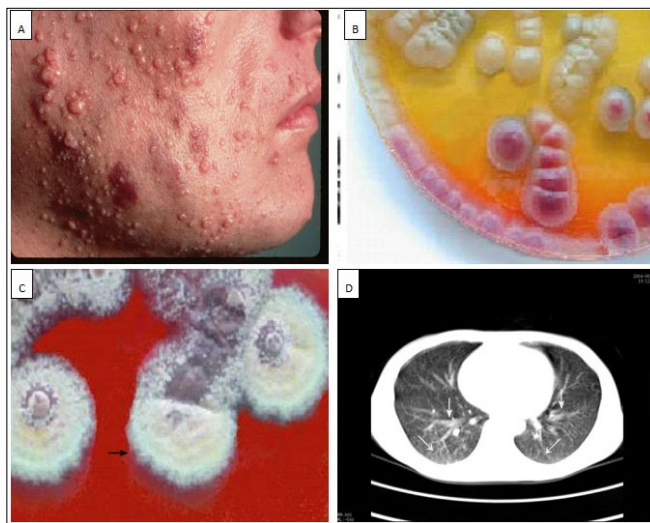


Figure 8. AIDS merged skin herpes zoster. **A:** Lesions of cheek; **B, C:** Result of blood culture; **D:** Result of lung CT.

↓: high density of shadow

HIV-associated seborrheic dermatitis

Case 1, a female, 28 years, was definitely diagnosed as AID by CDC. Quantity of CD4+ T cell was 35 μ l. Multiple nodular swellings were fund in back, forearm and ankle (**Figures 9A and 9B**). Large of swelling cells were extensively located around of sebaceous by histopathologic analysis (**Figures 9C and 9D**). Patients were in the acute phase of HIV-associated seborrheic dermatitis.

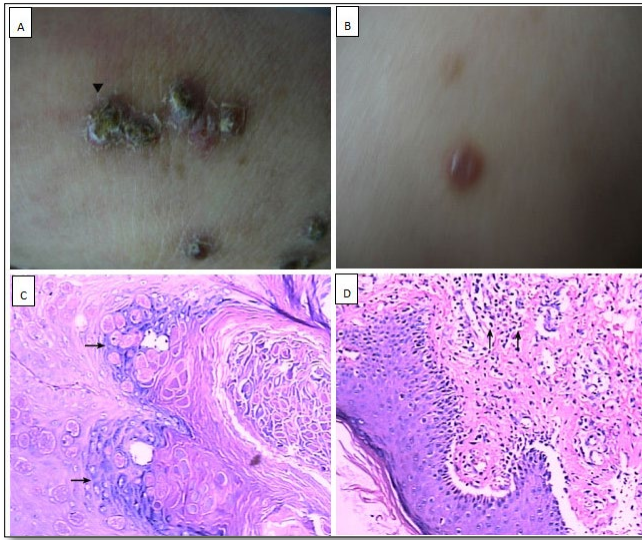


Figure 9. AIDS merged skin seborrheic dermatitis. **A, B:** Lesions of skin; **C, D:** Results of skin HE staining.

DISCUSSION

Occurrences of HIV-related skin folliculitis eosinophilia are close related with HIV infection characterized by obvious increase of blood eosinophils, large number of eosinophil infiltration in hair follicles of skin [4]. As an autoimmune disease, fungal infections can result in an inhibitory role on antigen exposure of body that may cause a severe hypersensitive effect. So, hidden antigen exposure of sebaceous glands can cause acidophilic granulocyte infiltration [5]. Noteworthy, only symptom analysis of skin without pathology, HIV-related skin folliculitis eosinophilia is often regarded as damp pestilence, allergic dermatitis, neurodermatitis that is often cause an event of misdiagnosis. In addition, it is necessary to distinguish HIV-related skin folliculitis eosinophilia from drug eruption. Drug eruption is generally divided into non anti-ADIS drug eruption and anti-ADIS drug eruption. Widely distributed rash in the skin is one of obvious features of non-anti-ADIS drug eruption. Anti-ADIS drug eruption can be further divided into mild type and severe type, former is often occurred in the trunk and limb that mainly show features of measles, later one exhibits features of Steven-Johnson syndrome as well as liver injury [6,7].

Infection of *S. aureus* can result in folliculitis, abscess and pustular sore of skin. Incidence of these complications is significantly increased in AIDS patients compared with that of normal people, mainly caused by *S. aureus* infection in AIDS patients. *S. aureus* has a higher opportunity of colonization than that of normal group with respect of serious impairment of skin mucous barrier and neutrophil function defect caused by HIV infection [8]. In the early stage of HIV infection, no special characterizations are observed. Along with advancing of HIV infection, except of

S. aureus infection, streptococcus, *S. epidermidis*, *Pseudomonas* spp. and *Escherichia coli* can also enter into body and bring about a threat on immunity. Therefore, serious skin lesions, multiple site complications, high-degree of recurrence and drug resistance can be detected [9].

Superficial fungal infections of AIDS often show ringworm of body, tinea cruris, tinea manuum, Athlete's foot, tinea capitis and onychomycosis [10,11]. Superficial fungal infection is a very common phenomenon in AIDS patients. Characterizations of most patients are similar with that of non-HIV-infected population. If two and/or more pathogens simultaneity invade into body, some special features such as skin ulcers, abscesses and skin necrosis and skin lesions are observed that should cause a difficult for treatment [12]. Deep skin infection of cryptococcus may cause mortality of normal population, also be one of the common reasons of death of AIDS patients [13]. Infection of cryptococcosis can result an injury of central nervous system, lungs, skin and bone. In addition, cryptococcus can spread into all the tissues and organs of body by blood circulation [13]. Skin lesions are mainly occurred in face, head, trunk and limbs. Noteworthy, contagious soft wart pimples, such as skin lesions, nodules, plaques, pustules, abscess and ulcer are mainly fund in trunk and limbs [14,15].

In the AIDS patients, infection of *P. marneffei* can cause a damage on mono-nuclear macrophage that in turn lead to a widely dissemination of body and high mortality. HIV-related complication of *P. marneffei* infection is one of the most common opportunistic infections in AIDS patients in Southeast Asia and southern region of our country, such as Guangxi and Yunnan [16]. Patients show fever, anemia, swelling of liver and enlargement of spleen lymph node, weight loss and pulmonary symptoms, 71% of them should undergo skin complication [17]. Skin lesions are mainly occurred in the face, upper trunk and limbs, and characterized by necrotic papules, infected papules, nodules, acne-like lesions, abscesses and ulcers [18]. Nevertheless, necrotizing papules are regard as marker of HIV-related skin disease of *P. marneffei* infection. As to skin complication, it is important to pay attention to other organ damage derived from *P. marneffei* infection in the process of treatment.

Herpes simplex virus (HSV) is divided into two groups including HSV-1 and HSV-2. In the HSV-1, lesions are occurred in mouth, nose and other parts of body, HSV-2 in reproductive organs [19]. Clinical studies have demonstrated that early onset of herpes simplex has a 2~12 days of latency, which is emerged in the mouth and fund in skin mucosa junction of mouse and nose. In where, serious symptoms including of appearance of stigmata, generation of cluster small bubbles, formation of erosion and blister of broken bubbles, deposition of pigment and itching or burning are observed [20]. In the recurrent herpes simplex, cluster small bubbles can be repeatedly occurred in the same region derived from some stimulate factors such as cold and

menstrual period [21]. Genital herpes is occurred in the genital organs that is associated with transmit by sexual contact. During whole course of AIDS, herpes simplex virus has a rich opportunity to induce an injury on cells. In the early stages of HIV infection, manifestations of herpes simplex virus infected patients are similar with that of non-HIV infected ones [20,21]. In advanced process of AIDS, herpes simplex infection often shows a high-frequent recurrence, a long course of ill, a wide range of lesions, a high occurrence of ulcers and necrosis and obvious drug resistance. Meanwhile, infection of genital herpes can result in a significant increase of HIV dissemination.

Incidence of herpes zoster virus infection is the highest among of HIV-associated complications, 26.4% of them is occurred in the stage of HIV infection, 73.6% of them in the AIDS stage [22]. A rapid progression of ill course is observed, it only experience 2 or 3 days from onset of obvious pain occurrence derived from a small amount of erythema and papules to complications of whole nervous system. Meanwhile, clustered blister, bulla, blood blister, necrosis are found in the surface of erythema. Obvious scars are formed on healing. Patients have other symptoms of all body, such as fever, tiredness, and so on [23].

Seborrheic dermatitis is a chronic spilled sebum that is associated with the overgrowth of *M. furfur*. Skin lesions are occurred in the regions of spilled sebum of head, forehead and nasolabial. Greasy scales are formed on the surface of erythema with itching [24]. As to seborrheic dermatitis of AIDS patients, skin lesions are often detected in the face, chest, back and limbs, even whole body. Generally, seborrheic dermatitis is regarded as the first HIV-related complication of AIDS patients [25].

Diagnose of HIV-associated skin complications is one challenge work with respect of complex etiology and diverse symptoms. In the current study, combination of pathology and microbiology is contribute to elucidate HIV-related skin complications at early stage and take measure preventing occurrence of these complication. Noteworthy, pathogenic infections can cause a threat on other organs because of low immunity of AIDS patients. Therefore, multiple strategies should be applied in the clinical to understand characterizations of HIV-associated skin complication.

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