DERMATOLOGIC MANIFESTATIONS IN HIV: UNVEILING OPPORTUNISTIC INFECTION

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Clinical practice, HIV-infected patients can be hospitalized for many problems. Especially in patients with late clinical presentation, differential diagnoses are often relatively broad. Besides the clinical symptoms and abnormal laboratory results, skin lesions are common problems in these patients. Cutaneous lesions (if they exist) range from typical to atypical and are crucial and valuable clues for diagnosis. In this article, we review the manifestations and importance of cutaneous lesions that present in HIV-infected patients with opportunistic infections.

Keywords: *Cskin lesions, HIV, opportunistic infections*

"The earth has a skin, and that skin has diseases; one of its diseases is called man."

Friedrich Nietzsche (1844-1900)

INTRODUCTION

In the middle of 1981, many outbreaks of *Pneumocystis* jiroveci pneumonia and Kaposi's sarcoma were reported in previously healthy homosexual men in New York and California, United States of America. Notably, Kaposi's sarcoma was a rare skin cancer that was seldom recorded before. Over forty years since the first AIDS cases were reported, skin disorders have been a common problem in persons living with HIV.

EPIDEMIOLOGY

In the pre-HAART area, skin disorders and diseases were frequent in HIV-infected patients. According to many previous researches, about 90% of HIV-infected patients had at least one skin disorder[1]. Nowadays, in the HAART area, the frequency of many opportunistic infectious diseases (including skin diseases or infectious diseases with skin manifestations) has been declining.[2] However, newly HIV-diagnosed patients with late clinical presentation are more common in developing countries than in developed countries. As a result, skin problems are more frequent in HIV-infected patients in resource-limited countries. In some circumstances, a chief complaint of HIV-infected patients is a skin disorder. In addition, patients can hospitalized with many other symptoms, but mucocutaneous disorders are concurrent reported problems.

Theoretically, skin disorders can appear in HIV-infected patients at any clinical stage. It should be emphasized that mucocutaneous lesions tend to be more common in patients with CD4 below 200/ mm^3 and naïve ART newly HIV diagnosed patients2. Persons living with HIV have very diverse skin lesions from typical to atypical due to many aetiologies. These lesions are not only aesthetic problems but also valuable diagnostic clues suspected of many serious diseases.

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Table 1. Clinical stage of HIV infection and corresponding skin disorders

Clinical stage of HIV infection	Diseases/Syndromes	Cutaneous lesions	Mucocutaneous lesions
1	Asymptomatic Persistence generalized lymphadenopathy		
2	Moderate unexplained weight loss (< 10% body weight)		
	Recurrent respiratory tract infections		
	Zona	x	
	Recurrent oral ulceration		x
	Angular cheilitis		x
	Papular pruritic eruption	x	
	Seborrheic dermatitis	x	
	Fungal nail infection	x	
3	Unexplained weight loss (> 10% body weight)		
	Unexplained chronic diarrhea for ≥ 1 month		
	Unexplained persistence fever (> 37.6oC intermittent or constant fever)		
	Persistence oral candidiasis		x
	Oral hairy leukoplakia		x
	Pulmonary tuberculosis		
	Severe bacterial infections		
	Acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis		x
	Unexplained anemia (< 8 g/dL), neutropenia (< 0.5 x 109/L) or chronic thrombocytopenia (< 50 x 109/L)		
4 (AIDS)	HIV wasting syndrome		
	Pneumocystis pneumonia		
	Recurrent severe bacterial pneumonia		
	Chronic herpes simplex infection	x	x
	Esophageal candidiasis (or candidiasis of the tracheal, bronchi, or lungs)		x
	Kaposi's sarcoma	x	x
	Cytomegalovirus infection (retinitis or other organs)		
	CNS toxoplasmosis		
	HIV encephalopathy		
	Extrapulmonary cryptococcosis, including meningitis	x	
	Disseminated nontuberculous mycobacterial infection	x[a]	
	Chronic cryptosporidiosis with diarrhea		

Clinical stage of HIV infection	Diseases/Syndromes	Cutaneous lesions	Mucocutaneous lesions
	Chronic isosporiasis		
	Chronic isosporiasis		
	Disseminated mycosis (talaromycosis, histoplasmosis, coccidioidomycosis)	x	x[b]
	Recurrent nontyphoidal Salmonella bacteremia		
	Lymphoma (cerebral or B-cell non-Hodgkin) or other solid HIV-associated tumors	x[d]	x[d]
	Invasive cervical carcinoma		x
	Atypical disseminated leishmaniasis	x	
	Symptomatic associated nephropathy or symptomatic associated cardiomyopathy		

Note: a Sometimes chronic ulcerative lesions appear on the skin with a positive AFB smear (cutaneous tuberculosis); b Central necrotic and umbilicated lesions are seen on the skin (lesions are seen on the oral mucocutaneous but rarely); d Sometimes skin lesions present in some cases with skin lymphoma (cutaneous lymphoma).

CLASSIFICATION

Besides Kaposi's sarcoma, there are 56 other cutaneous disorders believed to be related to HIV/AIDS3. These lesions can progress disseminated or become atypical because of the patient's severe immunosuppression. Even with a dermatologist, a definite diagnosis is not always confirmed in the first clinical examination.

Skin disorders in HIV-infected patients can be due to many different etiologies, from viruses, bacteria, and parasites to fungi. In addition, these cutaneous lesions are not always due to infection. Many other conditions can be the culprits that cause skin damage, such as cancer, autoimmune diseases, and skin reactions related to drugs. Currently, there is a growing body of evidence that immune dysregulation linked to HIV infection is a direct cause of skin disorders. Consequently, the spectrum of skin disorders in HIV-infected patients includes two groups: primary HIV-related skin disorders and secondary mucocutaneous signs of HIV infection[4].

Table 2. Classification of HIV-1 related skin pathology[4]

Primary manifestations	Secondary manifestations	
	Infectious	Neoplastic
- Seborrheic dermatitis - Xerosis - Atopic dermatitis - Eosinophilic folliculitis - Psoriasis - HIV1-related pruritus - Drug-induced	- Herpes simplex - Varicella zoster - HPV infection - Molluscum contagiosum - S.aureus infection Folliculitis Bullous impetigo Ecthyma - Mycobacterial cutaneous infection - Bacillary angiomatosis - P. aeruginosa cutaneous infection - Candidiasis - Dermatophyte infection - Histoplasmosis - Cryptococcosis - Pneumocystis	- Kaposi's sarcoma - T cell lymphoma - Basal cell carcinoma - Squamous cell carcinoma

Each classification method for skin lesions in HIV-infected patients is helpful because it provides different approaching perspectives for physicians. Nonetheless, we believe skin disorders classification is based on pathophysiology, and association with the degree of immunodeficiency is probably familiar to infectious disease specialists. Therefore, this classification for skin lesions is presented more detail below.

Lesions associated with opportunistic infection

a. Invasive fungal infection

In HIV-infected patients with late clinical presentation, invasive fungal infections are serious diseases that can be life-threatening. Most cases have the number of CD4 below 100/mm^3. In Vietnamese HIV-infected patients with invasive fungal infections, two common pathogens are *Cryptococcus spp* and *Talaromyces marneffei* (formerly known as *Penicillium marneffei*)[5]. In addition, *Histoplasma* capsulatum has also been reported occasionally in isolated cases. While *Cryptococcus* is a ubiquitous fungus, Talaromyces marneffei is an endemic pathogen in Southeast Asia. Nowadays, the prevalence of Histoplasmosis in Viet Nam may be underestimated because of the lack of optimal diagnostic tools.

Most Talaromycosis and Histoplasmosis cases in persons living with HIV have symptoms of prolonged fever, hepatomegaly, splenomegaly, lymphadenopathy, and anemia[5]. Although these signs are quite common, they are not completely specific to invasive fungal infections. Disseminated mycobacterial infection cases also present similar symptoms. In these circumstances, skin lesions are crucial clues that can suggest the diagnosis of invasive fungal infection.

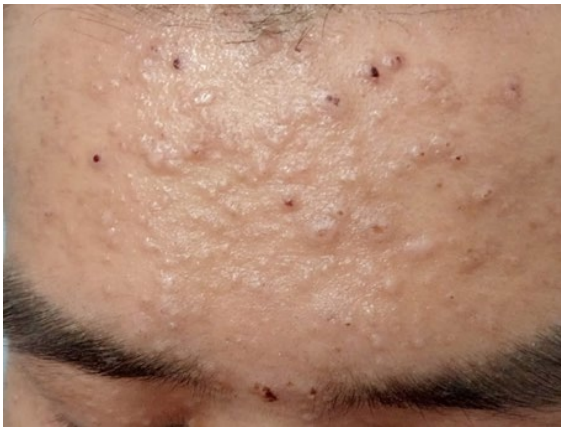


Figure 1 (left). A typical skin lesion of Talaromycosis. Central necrosis and umbilicated lesions are present in the forehead area. Notably, late-stage skin lesions are central necrosis papules.

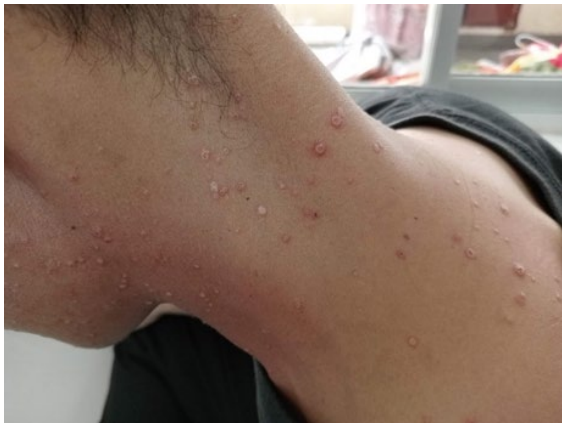


Figure 2 (right). A typical skin lesion of Talaromycosis. Early-stage lesions are central concave papules on the neck and nape. Another name for this type of lesion is a molluscum contagiosum-like lesion.

According to many research studies, about 70% of cases with *Talaromyces marneffei* infection have skin lesions[5]. These lesions usually appear first on the face and neck. After that, lesions spread to the trunk and limbs. However, typical lesions of Talaromycosis (central necrosis and umbilicated papules) are present in only 80% of cases with skin lesions. Therefore, a physician should not rule out Talaromycosis if HIV-infected patients have no or atypical skin lesions.

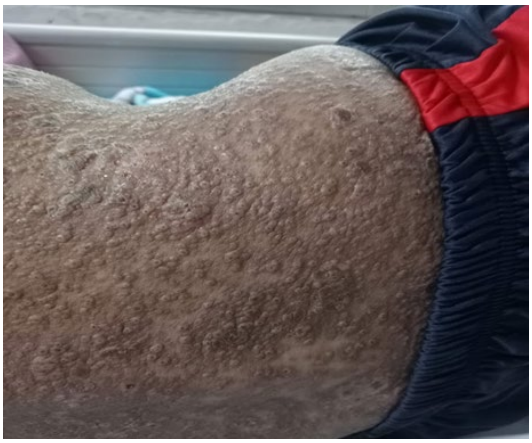


Figure 3A (left). A severe case of Talaromycosis. He had 2 months of history with wasting syndrome, anemia, skin lesions and isothermal. He was examined many times at Dermatology Hospital with the diagnosis of psoriasis. After he was hospitalized at the Hospital for Tropical Diseases, *Talaromyces* marneffei were isolated from skin lesions and blood culture. This case has atypical lesions of Talaromycosis because many skin lesions are umbilicated but have no necrosis. A special feature shows that these lesions are very dense and tend to be hyperkeratotic. Besides, his skin had hyperpigmentation.

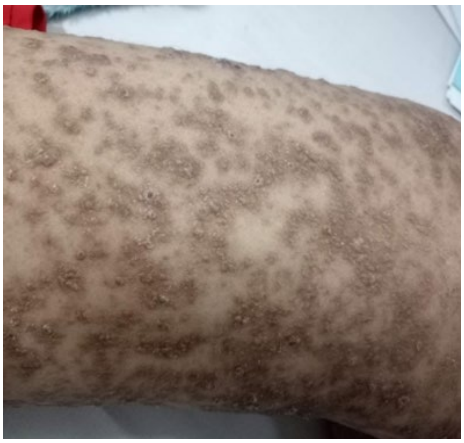


Figure 3B (left). (the same patient as in Figure 3A): He was treated with Amphotericin B infusion in the induction phase (14 days) and Itraconazole in the consolidation phase. After six weeks, most skin lesions improved significantly.

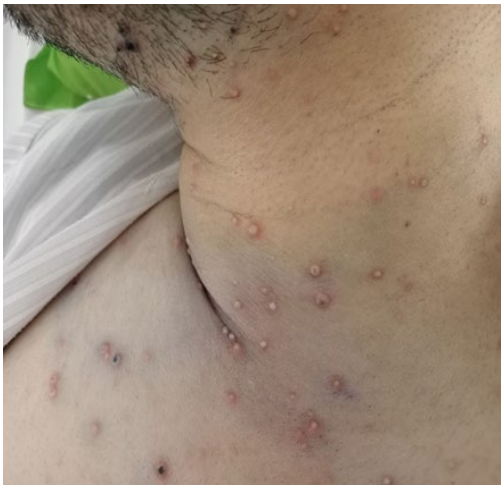


Figure 4 (left). Atypical skin lesions of Talaromycosis. A male patient had been diagnosed with chickenpox by a private hospital. After 5 days of treatment with oral acyclovir, his symptoms did not improve. Therefore, he was transferred to our hospital. His skin lesions have a form similar to pustules, but *Talaromyces* marneffei was isolated from these lesions.

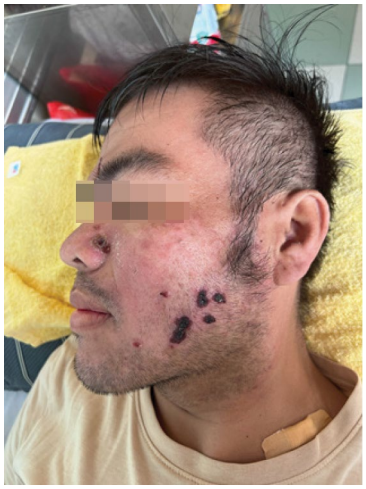


Figure 5 (left). Atypical skin lesions of Talaromycosis. An HIV-infected patient has some papules scattered on the face and many skin lesions in the form of crusted patches in the center. Some lesions on the left half-face are larger than typical ones of Talaromycosis. His blood culture was negative, but *Talaromyces* marneffei was isolated from the skin lesion culture.

Papular skin lesions are a valuable indicator of Talaromycosis. In addition, papules may be noted on the mucosa (see Figure 6). This is a rare feature of lesions in patients infected with *Talaromyces marneffei*. After searching the medical literature, we found 8 case reports (including 14 patients) about Talaromycosis with oral and/or pharyngeal mucosa lesions[6,7].

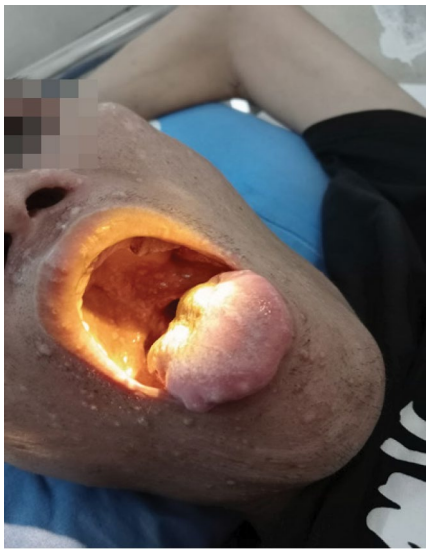
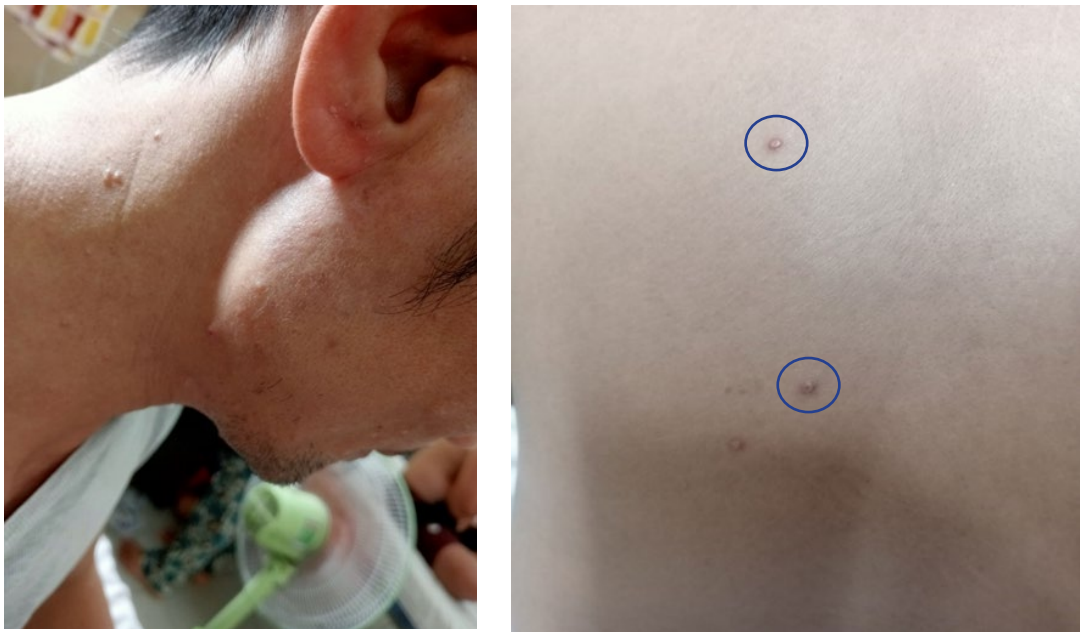


Figure 6. Mucocutaneous lesions of a Talaromycosis case

Typical skin lesions are on his face, and some are in his oral cavity. Many papular lesions with central concavity presented in the nasopharynx and soft palate. It should be noted that papules in the oral cavity are a rare feature of Talaromycosis.

b. Molluscum contagiosum infection

Infection with molluscum contagiosum virus often occurs in children under 5 years old. Skin lesions of this disease are called *mollusca*. This disease is usually benign in children, but lesions tend to progress disseminated in *immunosuppressive* patients (including persons living with HIV)[8]. Typical lesions in infection due to molluscum contagiosum are small papules (2 - 5 mm in diameter). They are waxy, skin-colored papules with umbilicated in the central lesions[9]. Erythema and scaling at the periphery of a single or several lesions may occur due to scratching or a hypersensitivity eczema-like reaction. It should be emphasized these lesions never have central necrosis. This manifestation is crucial to distinguishing them from skin lesions of some invasive fungal infections. In addition, the general condition of patients is relatively healthy in cases with molluscum contagiosum virus infection, in contrast to the severe clinical symptoms in patients with bloodstream infections caused by invasive fungus.



Figures 7A (left) and 7B (right) are two figures of the same patients: An HIV-infected patient who has been ART interruption for 3 years was readmitted. His chief complaint is hemiplegia on the left side. His MRI scan has many features that suggest progressive multifocal encephalopathy (PML). Some lesions on his face, neck, and back (located inside the blue circled area) are umbilicated papules, and no central necrosis exists. Skin lesions culture and blood culture are both negative. Two figures are lesions of molluscum contagiosum infection.

c. Human papillomavirus infection

Human papillomavirus (HPV), a sexually transmitted pathogen, is closely related to the risk of cervical cancer in women, anal and penile cancer in men, especially in homosexual men10-12. In HIV-infected patients, HPV infection tends to disseminate with many dense lesions. Besides aesthetic aspects, the risk of cancer progression is an issue that needs attention. However, skin lesions related to HPV infection are often ignored because they are usually located in private areas of the body. Skin lesions in the anogenital area caused by specific human papillomavirus (HPV) types are called anogenital warts. They are superficial skin lesions that usually appear three to six months after infection. An anogenital wart is a papule with a few millimeters in diameter. It is a flesh-colored papule with an irregular folded surface. Warts may join together to form plaques up to several centimeters across.

Noteworthy, HPV is not the only agent that causes lesions in the anogenital area. *Herpes simplex*, HIV, and Pox virus (cause molluscum contagiosum) are pathogens related to common viral infections of the perianal skin and anorectum9 (see clinical case in Figure 8).

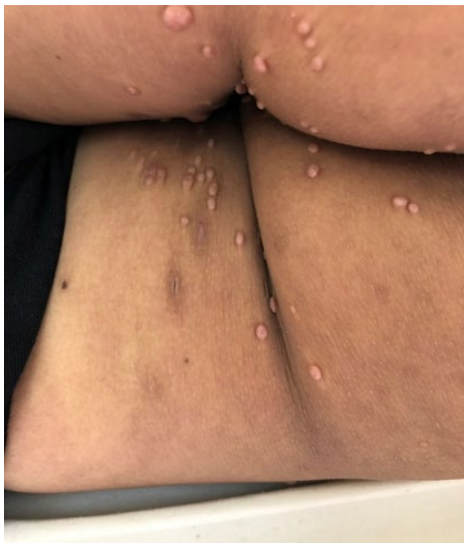


Figure 8. Perianal lesions in an HIV-infected patient

A homosexual man was admitted because of aphasia and weakness in his right arm. His MRI scan had some features that suggested progressive multifocal leuko-encephalopathy (PML). In addition, he had many skin lesions concentrated in the perianal area. This is a case of perianal skin lesions due to molluscum contagiosum virus.

Subtle central umbilication in some of these lesions (blue arrows) distinguishes this diagnosis from human papillomavirus.

d. Varicella zoster virus infection

Although chickenpox is benign to most children, varicella zoster virus cannot be eliminated from the body. This virus usually exists latently in the nerve ganglia[13]. Therefore, they can reactivate many years later, causing shingles (zona)[13]. Risk factors for zona have been recorded in the literature, including diabetes, cancer patients undergoing chemotherapy, patients using immunosuppressive drugs, and HIV-infected patients[14].

There are some special features of VZV infection in persons living with HIV. HIV-infected patients who have chickenpox or herpes zoster are a high-risk group for disseminated disease progression or complications[15,16]. As a result, HIV-infected patients usually need treatment with intravenous acyclovir, especially in patients with low CD4 (below 350/mm^3)[17]. In addition, persons living with HIV have a 15-fold higher risk of VZV reactivation than HIV-uninfected persons[18,19]. Another abnormal manifestation of VZV reactivation reported in immunodeficiency patients is disseminated shingles[20,21]. In the context of disseminated shingles, a patient has blisters scattered in many areas at distant locations.

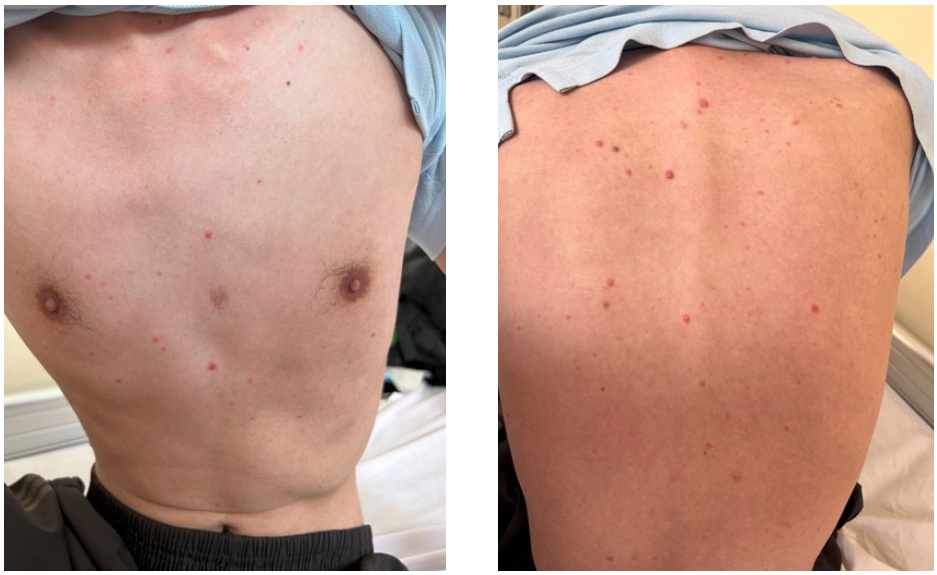


Figure 9A (left) and 9B (right) are two figures of the same patients: A newly HIV-diagnosed patient was admitted because of prolonged cough, chill, and weight loss. His CD4 count is very low (only 03/mm3). After 7 days in our hospital, he suffered from many skin lesions (Figures 9). His blisters were scattered in many areas at distant locations. He reported he had chickenpox two years ago. PCR with the sample from blisters was positive for VZV-DNA; hence, this patient is a case of disseminated shingles. CSF-PCR for VZV was negative. He was treated with acyclovir infusion (10mg/kg/day) for 14 days, and his symptoms improved completely.

e. Herpes simplex infection

Infection due to *Herpes simplex* (HSV type 1 or HSV type 2) is common in the general population[22]. However, these pathogens can survive persistently in the human body to create latent infection. Sometimes, reactivation of them causes herpes labialis (due to HSV-1) and genital herpes (mostly due to HSV-2)[22]. Reactivation of *Herpes simplex* virus can be more frequent, last longer, and cause serious consequences, especially in immunocompromised patients (including HIV-infected patients)[23-25].

There are many noteworthy points and these features exhibit differences of *Herpes simplex* reactivation in HIV-infected patients from non-HIV patients. Skin lesions due to *Herpes* simplex could be recurrent after stopping treatment with acyclovir[24]. Therefore, recurrence prophylaxis is probably necessary for patients with severe immunosuppressive conditions. In addition, the appearance and/or rapid progression of perianal ulcerative lesions could be an indicator of AIDS[25].

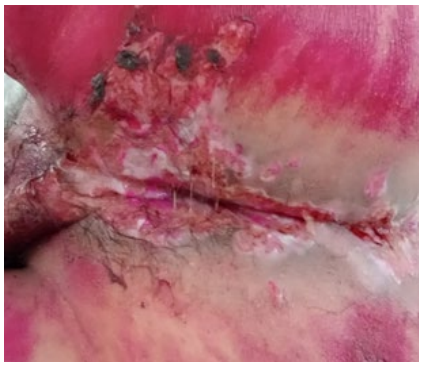


Figure 10A (on admission)

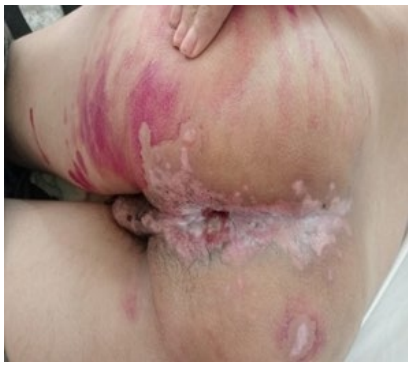


Figure 10B (after 10 days of treatment)

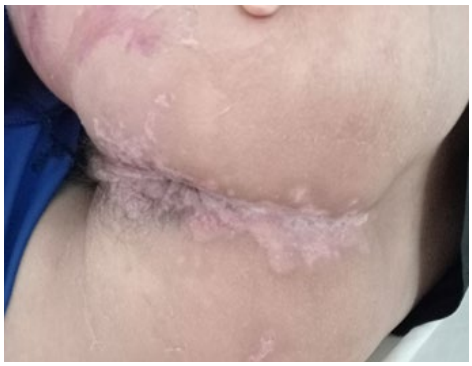


Figure 10C (one month after the second hospital discharge)

Figure 10A, B, and C belong to the same patient. A homosexual patient visited the Urology Department of Surgical Hospital because of large, ulcerated lesions in the perianal area. The lesions, which appeared one month ago, showed signs of fluid secretion and pain. He took care of the wound himself with red-eosin and NaCl 0,9%, but they did not improve. His HIV rapid test was positive, and he was transferred to our hospital. He was confirmed HIV infection (stage 4 with CD4 count number: 89/mm3), and Herpes simplex PCR was positive with the sample from perianal ulcerative lesions. Therefore, he was treated with acyclovir infusion (10 mg/kg/day), and his skin lesions improved significantly. After using 10 days of acyclovir, he continued to be treated with oral acyclovir (for the next 4 days) and was discharged. Three days after discharge, he started to use ART (TDF/3TC/DTG).

Three weeks later, his perianal lesions had reappeared. As a result, he was admitted to our hospital again. A PCR test for these lesions was positive for Herpes simplex. These manifestations suggested a relapse case of genital herpes; hence, we retreated him with intravenous acyclovir (10 mg/kg/day) for 21 days. After that, he was treated with oral valacyclovir (1000 mg/day, divided into two doses) for relapse prophylaxis. One month after the second hospital discharge, his perianal lesion did not reappear. Prophylaxis with oral valacyclovir was stopped after 3 months and he continued ART (Acriptega).

CONCLUSIONS

Nowadays, skin disorders are still common problems in persons living with HIV, especially in Vietnam. Mucocutaneous lesions have abundant causes, of which opportunistic infections are the leading culprits. Therefore, dermatologic manifestations are useful clinical markers in identifying and suggesting many potential causes.

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