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Clinics in Dermatology

Cutaneous manifestations associated with HIV infections: A great imitator

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Abstract HIV is associated with an increased incidence of mucocutaneous disorders, with the overwhelming majority of HIV-infected individuals being afflicted with skin diseases during the course of the infection. Skin diseases in HIV patients are rarely fatal, but they have a significant effect on the quality of life. The immunologic stage of the infection and the use of highly active antiretroviral therapy (HAART) are the main elements that determine the spectrum of the mucocutaneous involvement. Many skin diseases may occur simultaneously in HIV patients, and the course of these diseases may or may not be different than it is in HIV-negative individuals. The unusual, severe, and different presentations of the mucocutaneous involvement make HIV one of the great imitators in dermatology.

Introduction

Cutaneous manifestations of HIV infection are common, and most HIV-infected patients experience skin diseases during the course of the disease.[1] Many dermatologic conditions may develop simultaneously in HIV-infected individuals, and they usually show an unusual and severe course. Dermatologic manifestations of HIV infection mainly include infectious, inflammatory, neoplastic, and treatment-associated conditions.

Infectious diseases

Viral infections

Primary HIV infection

Primary HIV infection, also known as acute retroviral syndrome, is usually asymptomatic; however, an acute febrile disease may be seen in two-thirds of HIV-infected individuals. This acute illness develops 3 to 6 weeks after exposure to the virus, usually lasts 1 to 2 weeks, and is often misdiagnosed as infectious mononucleosis. The clinical manifestations include fever, malaise, muscle pain, headache, lymphadenopathy, and a generalized maculopapular or roseola-like eruption that may involve the palmoplantar area reminiscent of secondary syphilis. Oral and genital mucosal lesions include erythema and ulcerations. Oral candidosis, which is usually considered to be a manifestation of advanced immune dysfunction, can also be seen in primary HIV infection.[2,3]

Human papilloma virus

Human papilloma virus (HPV) infection and its clinical manifestations are common among HIV-infected patients (Figure 1). Common warts can develop in unusual sites with unusual severity and can be very challenging to manage.[4] Classic regimens, including topical podophyllin and imiquimod or cryotherapy, may be ineffective, and more aggressive treatments, like surgical removal or intralesional cidofovir administration, may be needed.[4] HPV-associated dysplastic

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changes are also common in HIV-infected individuals. The progression of HPV-related anal or cervical lesions with severe dysplasia and squamous cell carcinoma occurring is strongly correlated with the level of immunodeficiency.[5] Homosexual men are especially at risk for developing anal high grade squamous epithelial lesion (HSIL) and squamous cell carcinoma.[6] In making the diagnosis of condyloma accuminatum, the possibility of HSIL and squamous cell carcinoma should also be considered.[4] HPV vaccination may prevent HPV-related conditions in HIV-infected individuals. The Centers for Disease Control and Prevention recommends HPV vaccination for all HIV-infected individuals who are 26 years old or younger.[4]

Acquired epidermodysplasia verruciformis (EV) or EV-like syndrome is another condition associated with HPV, particularly HPV-5 in HIV-infected patients. This usually presents with hypopigmented or pink macules, papules, and plaques in sun-exposed sites on the trunk and extremities. The lesions may resemble seborrheic keratosis and verrucae, as well as mimicking tinea versicolor. Although malignant transformation of the lesions of hereditary EV is well established, the potential risks of acquired EV are still unknown.[7]

Herpes simplex virus

Herpes simplex virus (HSV) infection (Figure 2) is the most common viral infection found in HIV-infected individuals, and as the CD4 count decreases, the prevalence of the infection may reach approximately 30% among HIV-infected patients.[3] Patients with HSV-2 infection are two to threefold as likely to transmit HIV. The clinical manifestations can be very atypical and treatment resistant, with chronic nonhealing ulcerations and verrucous lesions being the well-known atypical presentations. The ulcerations may be misdiagnosed as pyoderma gangrenosum, atypical mycobacterial infection, or even deep fungal mycoses,[8] as they can imitate verrucous carcinoma, deep fungal and mycobacterial infections, condyloma lata, condyloma accuminata, and pemphigus vegetans.[9]

Recently acyclovir resistance in HIV-infected individuals has become a common concern, possibly due to widespread use among patients. Intravenous foscarnet and intralesional cidofovir are the second-line options in acyclovir-resistant cases.[4]

Varicella zoster virus

Primary varicella zoster virus (VZV) infection in HIV-infected children and adults is usually severe and disseminated.

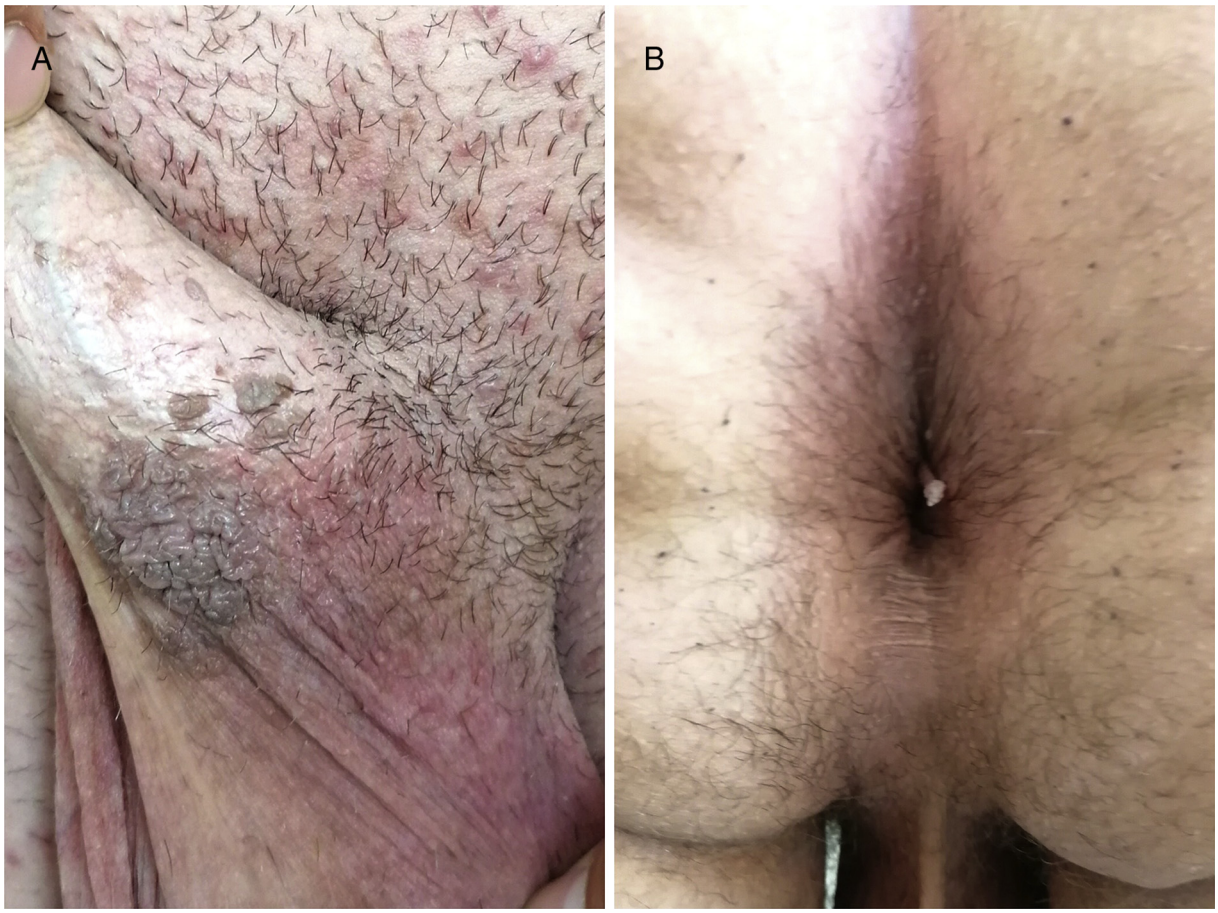

Fig. 1 Genital **(A)** and perianal**(B)** verrucae. (From Ahi Evran University, Department of Dermatology).

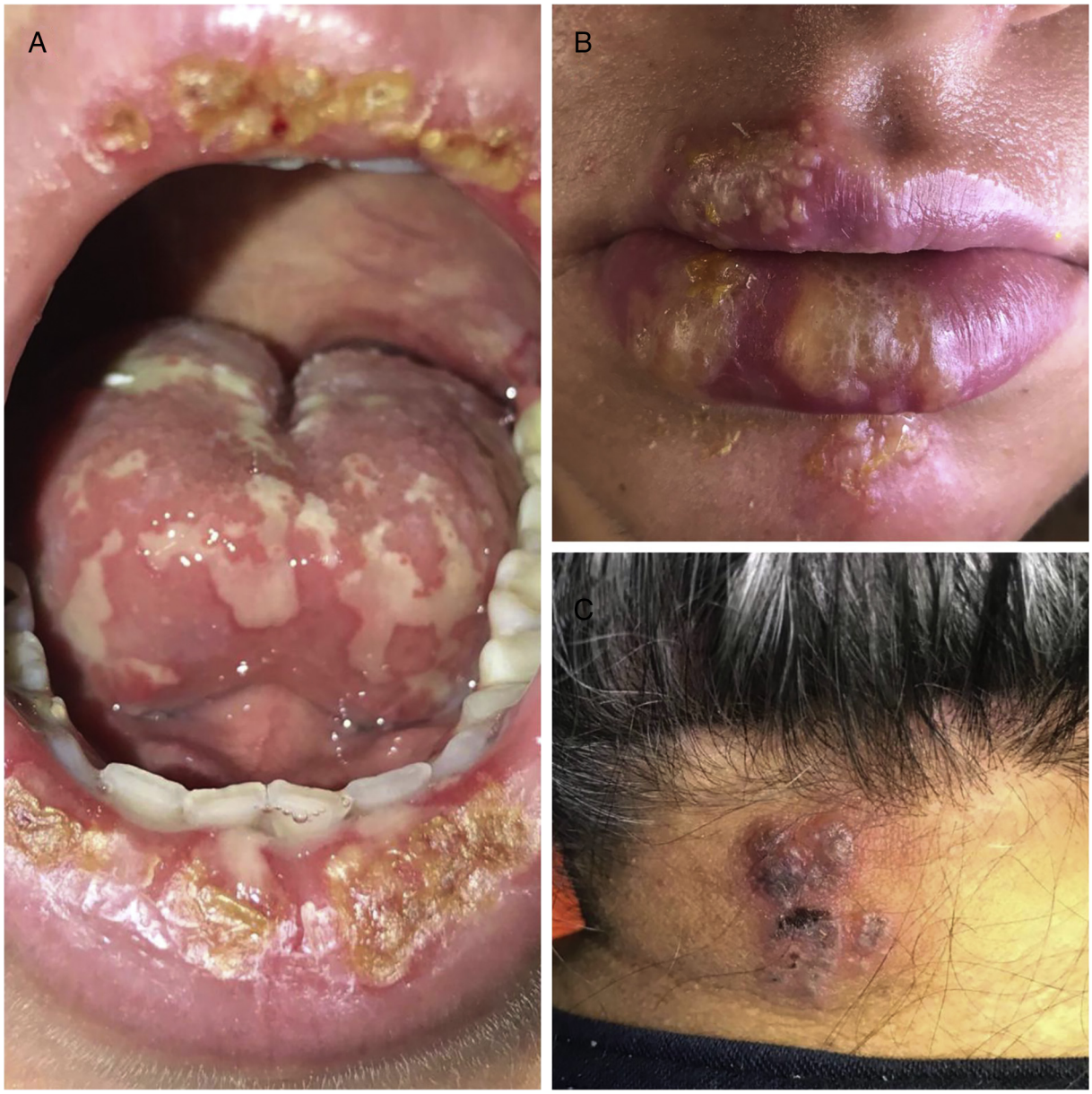

Fig. 2 Mucosal **(A, B)** and cutaneous **(C)** Herpes simplexital infections. (From Ahi Evran University, Department of Dermatology).

In addition to the cutaneous manifestations, pneumonia, pancreatitis, and encephalitis may occur.[10] With VZV reactivation, herpes zoster (HZ) (Figure 3) is remarkably increased in HIV-infected individuals, as is recurrent HZ.[11] The clinical presentations range from the usual vesicular eruption in dermatomal distribution to multidermatomal or disseminated necrotic and hemorrhagic lesions. Persistent verrucous, hyperkeratotic, and ecthyma-like lesions may mimic any number of bacterial infections, verrucae, pityriasis lichenoides, secondary syphilis, and vasculitis.[2,3]

HZ can be the initial manifestation of HIV infection and HIV testing is recommended in anyone younger than 65 years of age with HZ. It should also be kept in mind that VZV reactivation may reflect immune reconstitution after starting highly active antiretroviral therapy (HAART).[4]

HZ may also be characterized by dermatomal pain without skin lesions, a phenomenon known as zoster sine herpete (ZSH).[12]

Molluscum contagiosum

Molluscum contagiosum (MC) (Figure 4) is a common viral infection caused by a pox virus. The frequency is remarkably increased in HIV-infected individuals. Although MC usually has a self-limited course in immunocompetent hosts, this is not the case in HIV-infected individuals. Generalized, chronic, and recalcitrant lesions may occur, with giant and even verrucous

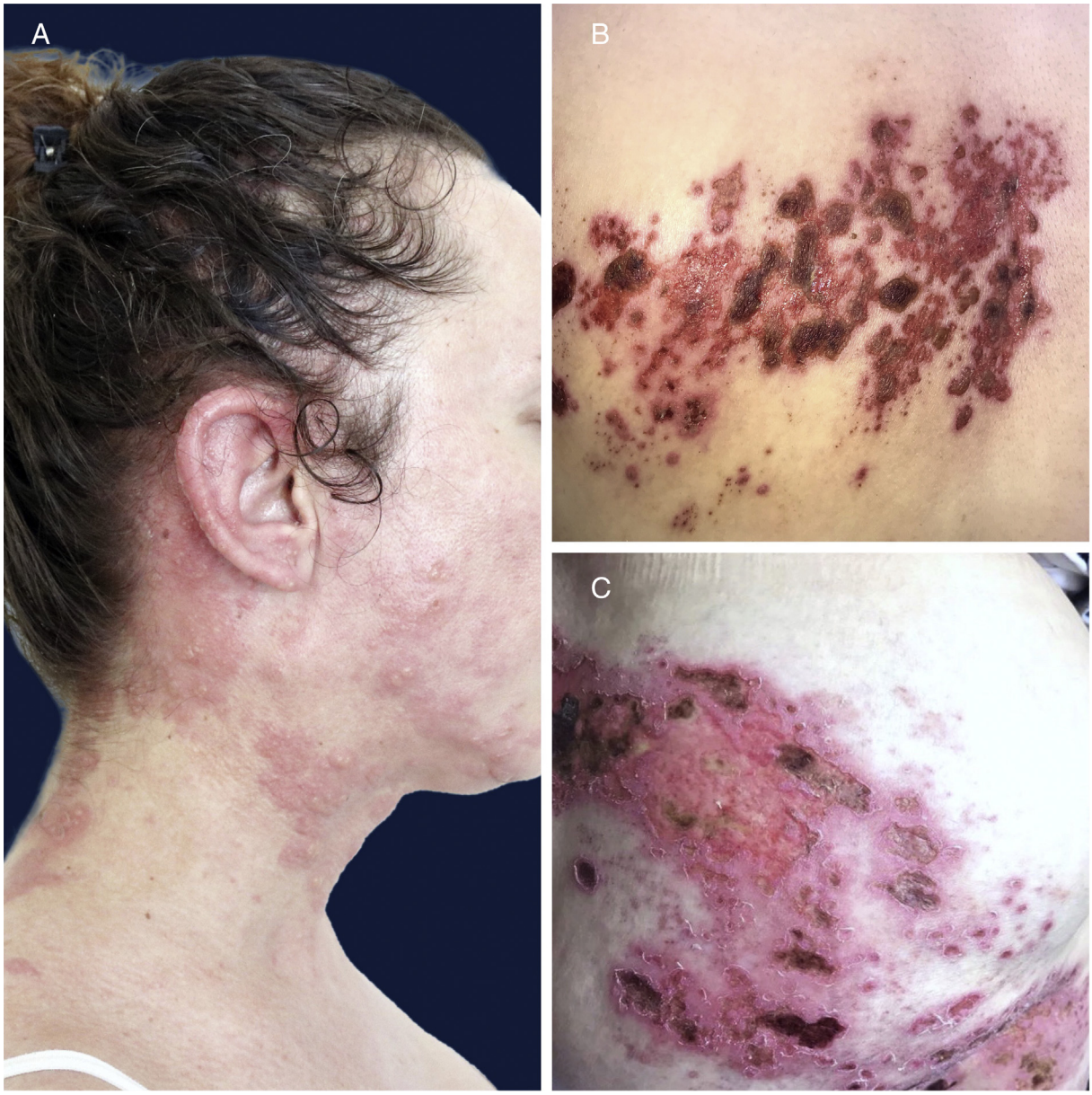

Fig. 3 Herpes zoster localized on the face, neck **(A)**, back **(B)**, and gluteal region **(C)**. (From Şişli Hamidiye Etfal Training and Research Hospital, Department of Dermatology (A, B) and Ahi Evran University, Department of Dermatology (C)).

lesions on the face developing. These atypical forms can imitate verrucae, basal cell carcinoma, keratoacanthoma, atypical mycobacterial infection, cryptococcosis, histoplasmosis, and penicilliosis. Histopathologic examination would be confirmatory.

Bacterial infections

Syphilis

Syphilis (Figures 5, 6) in HIV-infected individuals is associated with a significantly more rapid progression to tertiary syphilis and unfavorable treatment results.[13] Overlapping between the stages, multiple chancres and impaired serologic response (including high titers, false negative results, and delayed seroreactivity) may also be seen.

Bacillary angiomatosis

Bacillary angiomatosis (BA) (Figure 7), also known as epithelioid angiomatosis, is a rare angioproliferative disease, characterized by cutaneous and visceral vascular proliferation caused by *Bartonella henselae* or *Bartonella quintana.* BA was first described in HIV patients and tends to develop in patients with decreased CD4 counts; however, it is also known to occur in patients with non-HIV immunosuppressive conditions, including organ transplantation, chemotherapy, and hematologic malignancy. The cutaneous manifestations range from a few red or purplish papules to countless papular and nodular lesions, usually on the arms. There may be central ulcerations and bleeding in the nodular lesions. BA infection

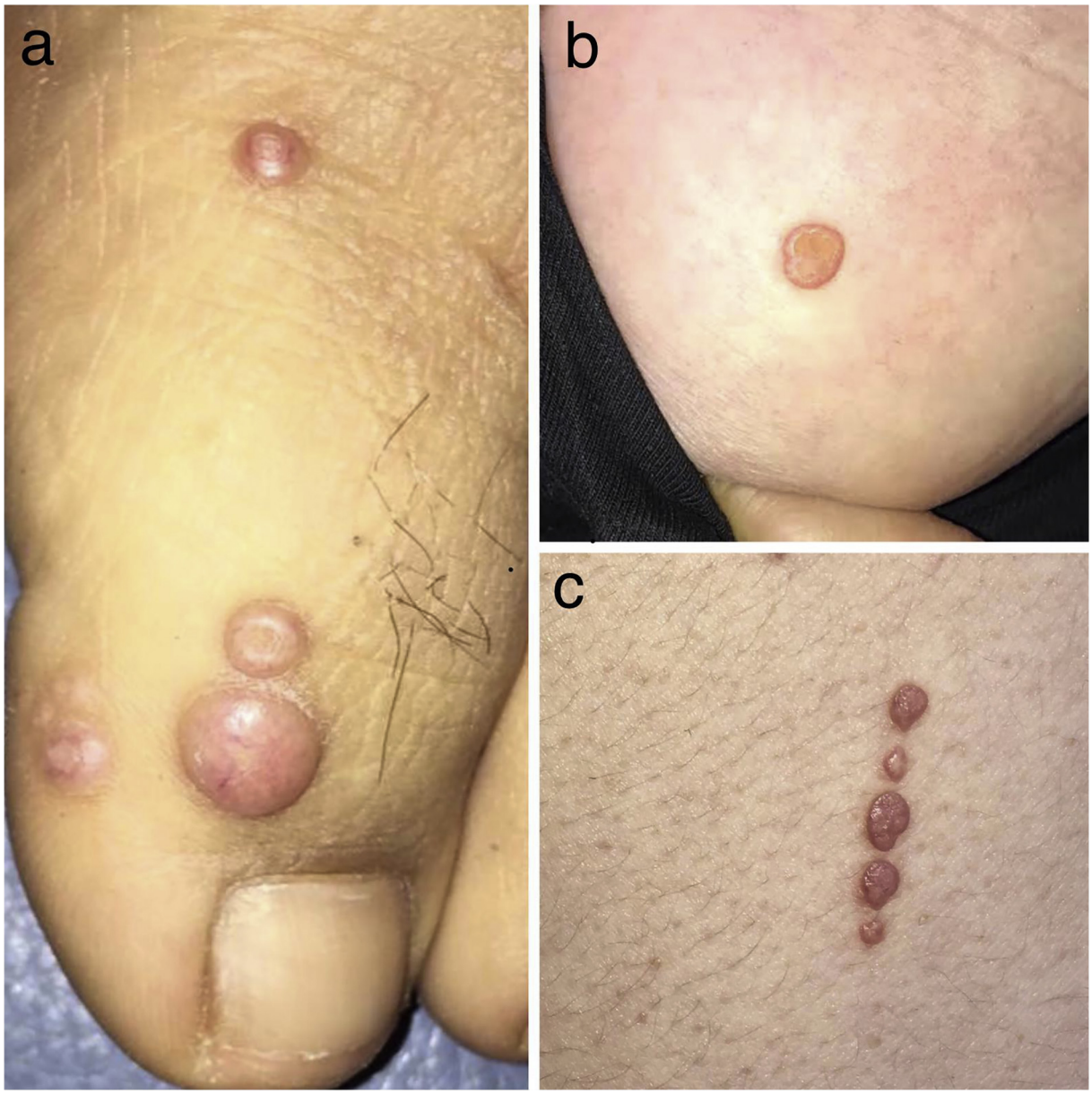

Fig. 4 Giant molluscum lesions on the dorsal surface of the foot **(a)** and breast **(b)**. Molluscum papules demonstrating the Koebner phenomenon **(c)**. (From Ahi Evran University, Department of Dermatology).

may be generalized and involve the oral mucosa, oropharynx, tongue, nose, and anogenital region. Cutaneous BA may imitate pyogenic granuloma, Kaposi's sarcoma, hemangiomas, and cutaneous metastasis.[14]

Fungal infections

Dermatophytosis

The incidence of dermatophyte infections in HIV-infected individuals is not significantly higher than those in immunocompetent individuals; however, the presentation will be more severe, atypical, and prolonged in HIV-infected individuals.[15] For example, tinea corporis (Figure 8) may have a more chronic course with coalescent hyperpigmented plaques mimicking contact dermatitis, mycosis fungoides, or sarcoidosis.[3] A clue for such infections may be proximal white onychomycosis.[16]

Candidosis

Candidosis is the most common opportunistic fungal infection, usually due to *Candida albicans*. This can be an initial manifestation of HIV infection. A low absolute CD4 count (especially lower than 200 cells/μL) is considered to be the major risk factor. The more common clinical manifestations on the skin may range from asymptomatic colonization to oropharyngeal candidosis (OPC), vulvovaginal candidosis, onychomycosis, esophagitis, and disseminated invasive candidosis. OPC is the most common form and

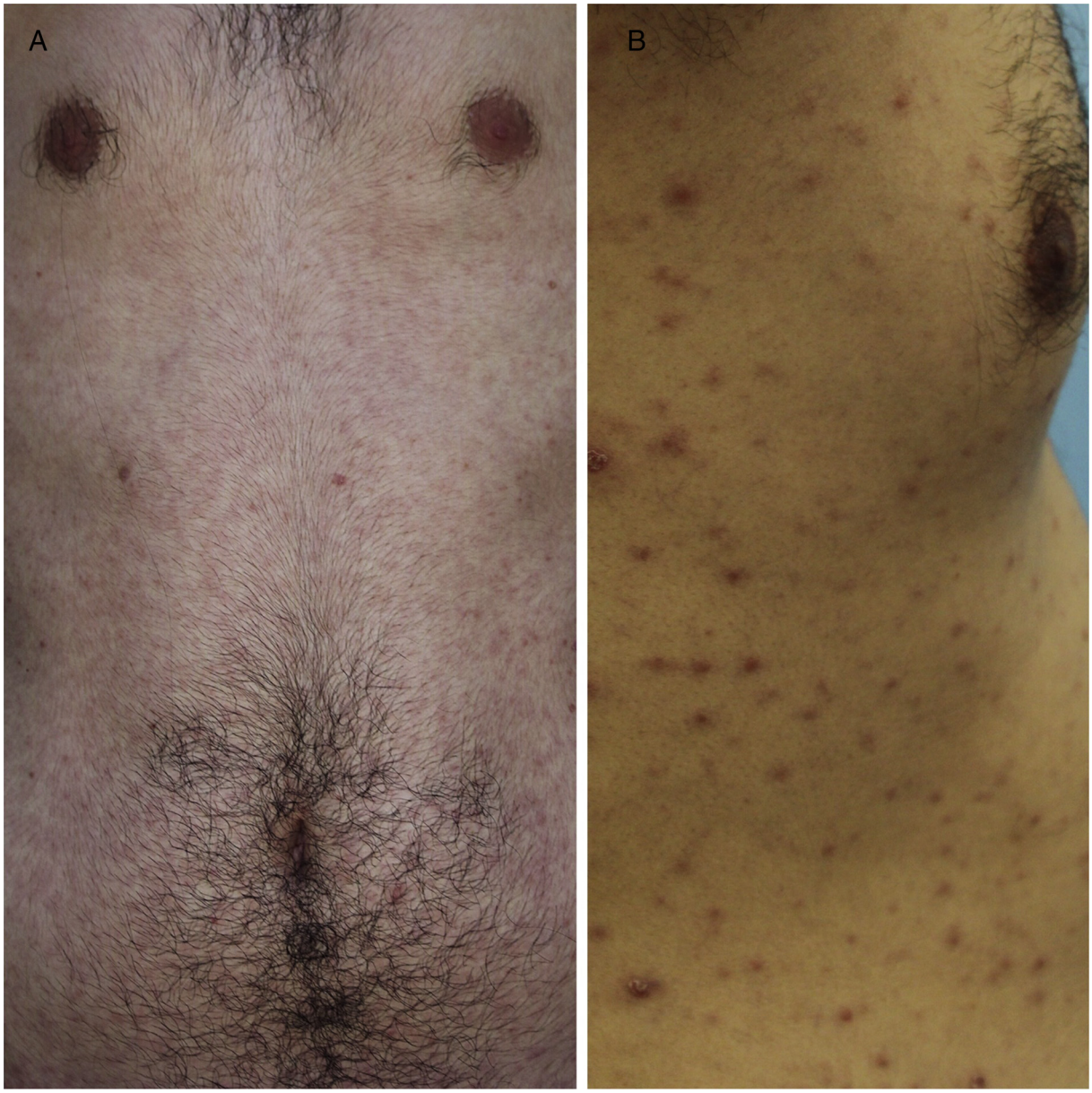

Fig. 5 Roseola syphilitica **(A)** and pityriasis rosea-like eruption of secondary syphilis **(B)**. (From Istanbul Medeniyet University, Department of Dermatology).

may present with pseudomembranous and erythematous lesions, as well as angular cheilitis.[17] Lookalikes may include aphthous stomatitis, lichen planus, leukoplakia, erythroplakia, and squamous cell carcinoma.

Cryptococcosis

Cryptococcosis is an opportunistic invasive fungal infection caused by an encapsulated yeast *Cryptococcus neoformans.* It is an important cause of mortality among HIV-infected individuals.[18] Primary cutaneous cryptococcosis is rare, and cutaneous involvement usually indicates systemic infection. Cutaneous lesions are nonspecific and may include papules, plaques, pustules, nodules, and ulcerations that may mimic MC,[3] along with pyogenic and nocardial abscesses, cutaneous lymphoma, basal cell carcinoma, cutaneous tuberculosis, syphilis, cutaneous metastasis, and histoplasmosis. Cutaneous cryptococcosis is often diagnosed by detection of the yeast on histopathologic examination.[18]

Histoplasmosis

Histoplasmosis, caused by *Histoplasma capsulatum,* has the ability to affect both immunocompromised and immunocompetent persons. Although it is usually asymptomatic and has a self-limited course in immunocompetent individuals, histoplasmosis in the HIV-infected patient is characterized by a symptomatic and disseminated infection in the overwhelming majority of the cases. Primary cutaneous histoplasmosis is extremely rare and usually occurs as a part of

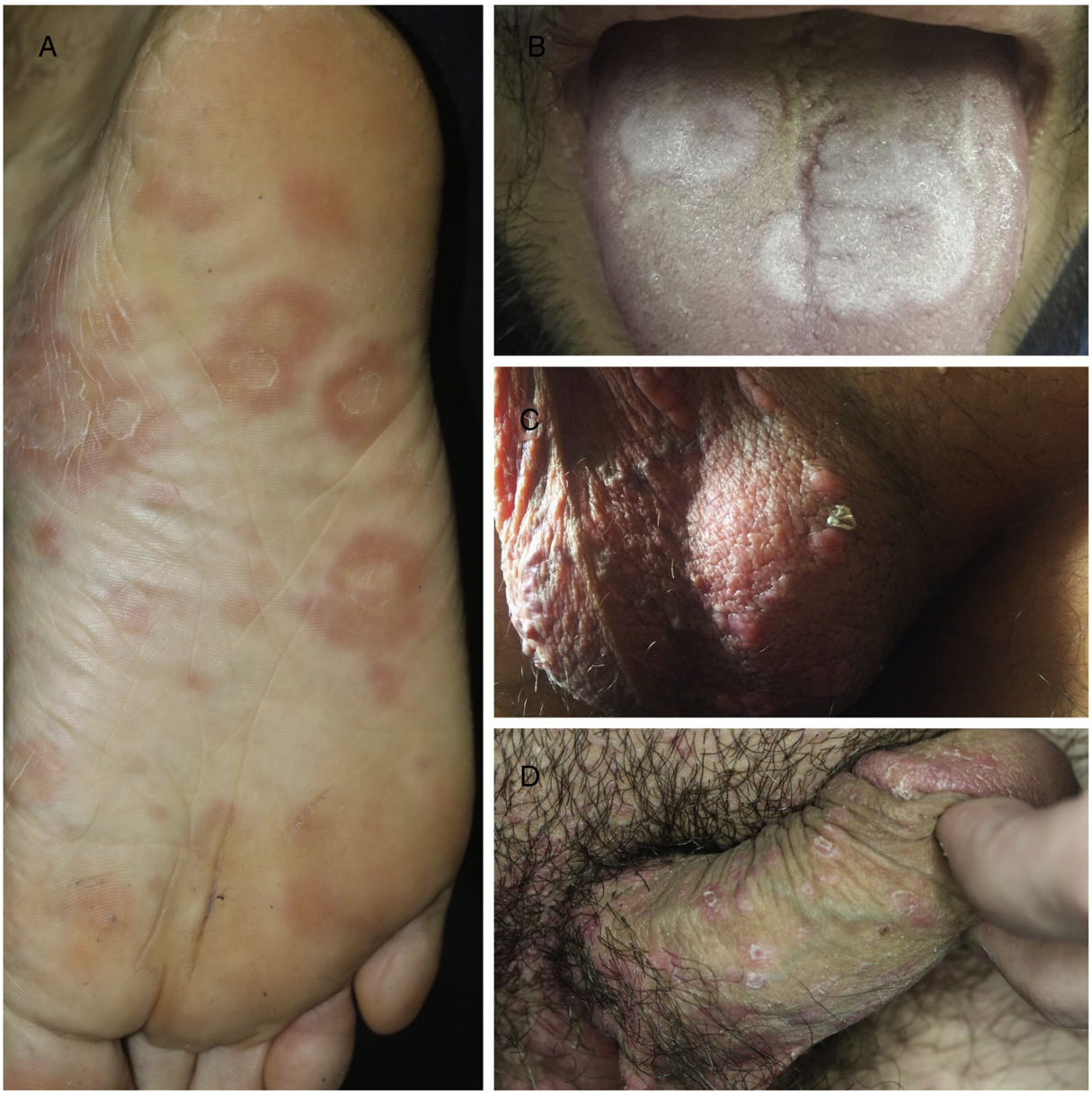

Fig. 6 Secondary syphilis demonstrating plantar maculopapular lesions **(A)**, plaque mucous **(B)**, scrotal papular lesions **(C)**, and penile papular lesions **(D)**. (From Istanbul Medeniyet University, Department of Dermatology) picture a should be reotated 180 degrees.

disseminated disease. Although the skin involvement may be nonspecific, diffuse erythema, papulopustular lesions, crusts, ulcerations, and psoriasiform lesions may be seen. Cutaneous histoplasmosis can mimic MC, pyogenic abscess, verrucae, erythema nodosum, cutaneous metastasis, and psoriasis. A high level of suspicion is essential for diagnosis due to the nonspecific clinical nature of the infection. Cutaneous histoplasmosis is usually diagnosed when a histopathologic examination shows the macrophages with multiple intracellular fungal spores.[19]

Pneumocystis jirovecii infection, penicilliosis, and coccidioidomycosis are the other fungal infections that may have a wide nonspecific spectrum of cutaneous manifestations in HIV-infected patients.

Parasitic infections

Crusted scabies

Crusted scabies (Figure 9) may occur in the setting of immunosuppression. In contrast to classic scabies, it presents with crusted and hyperkeratotic lesions on an erythematous base anywhere on the body. Itching is not prominent and may even be absent. The diagnosis may be confirmed by direct microscopic examination of a skin scraping; dermatoscopic examination may also be helpful.[20] Such an infestation can mimic a wide variety of dermatologic conditions, including acquired ichthyosis, hyperkeratotic dermatitis, psoriasis, contact dermatitis, mycosis fungoides, and even secondary syphilis. Misdiagnosis is often a common occurrence.

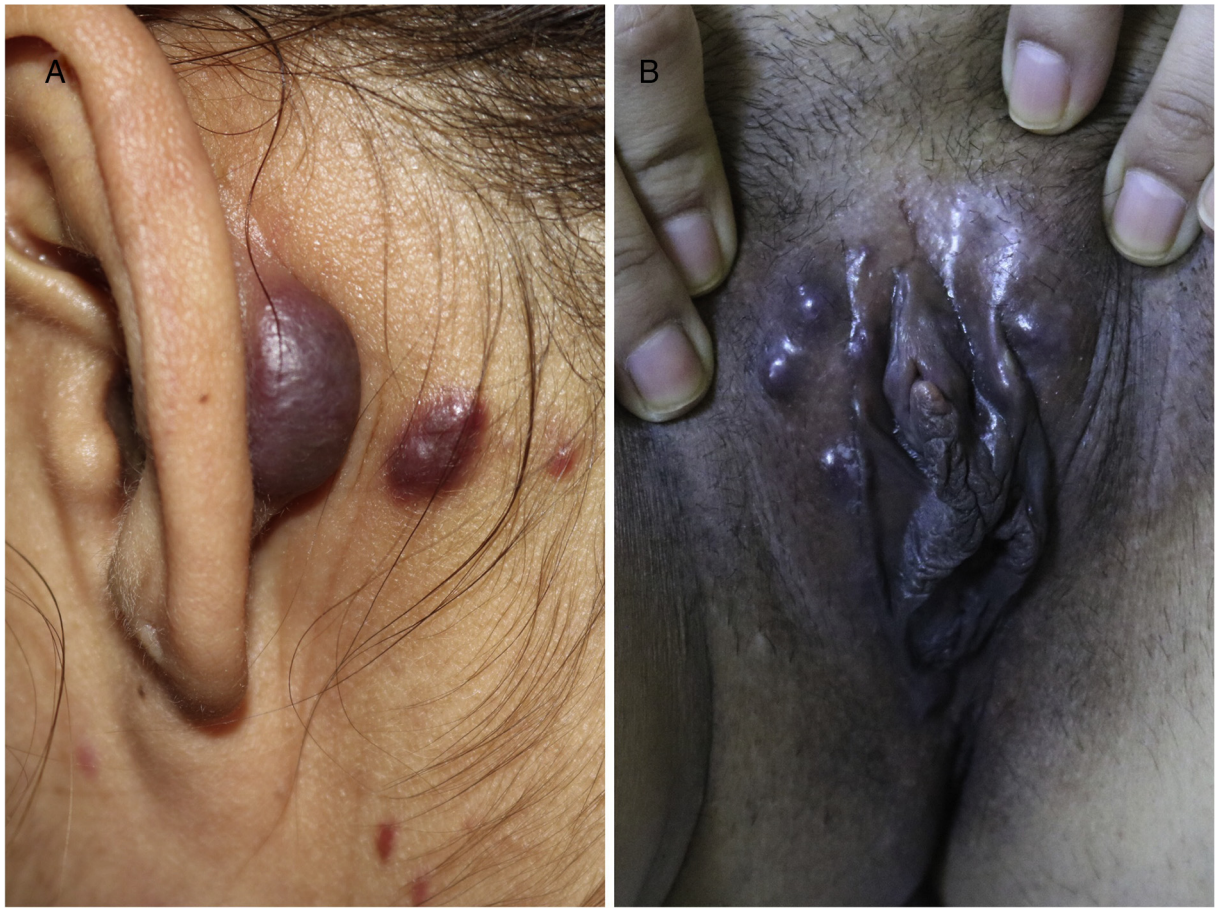

Fig. 7 Bacillary angiomatosis localized on the postauricular **(A)** and vulvar **(B)** regions. (From Şişli Hamidiye Etfal Training and Research Hospital, Department of Dermatology).

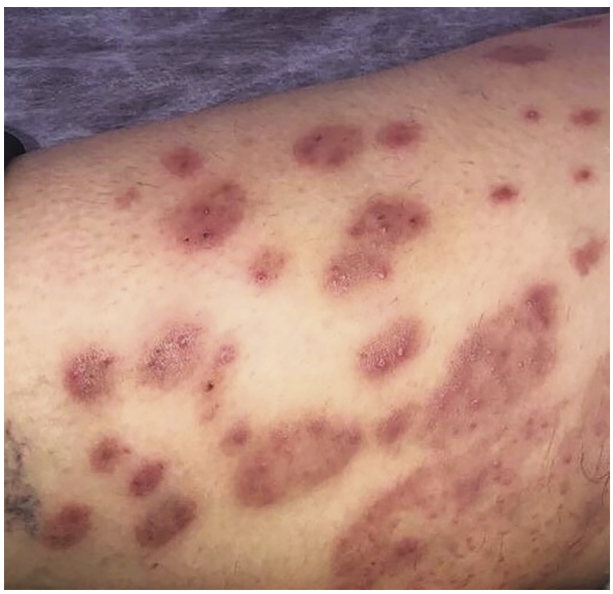

Fig. 8 Tinea corporis presenting with multiple annular plaques on the thigh. (From Ahi Evran Universiry, Department of Dermatology).

Table 1 summarizes the clinical features and differential diagnosis of HIV-related infectious conditions.

Inflammatory conditions

Psoriasis

Psoriasis (Figure 10) may be exacerbated or newly diagnosed in HIV-infected patients; however, it typically tends to present in the setting of advanced immunodeficiency. The diagnosis and management of HIV-related psoriasis may be very challenging because many comorbid skin disorders in HIV-infected individuals may imitate psoriasis; furthermore, the clinical nature of psoriasis tends to be much more severe and refractory to treatment in HIV-infected individuals. The characteristic hallmark of HIV-related psoriasis is that several phenotypical variants may coexist in the same patient. A high level of suspicion and a careful history is necessary for accurate diagnosis of psoriasis in HIV-infected individuals.[21] The histopathologic features of HIV-related psoriasis may be identical to classic psoriasis; however, the presence of numerous plasma cells should raise the possibility of associated HIV infection.[21] Treatment responses in HIV-infected individuals are comparable to those observed in HIV-negative patients with psoriasis. The first-line treatments, such as topical

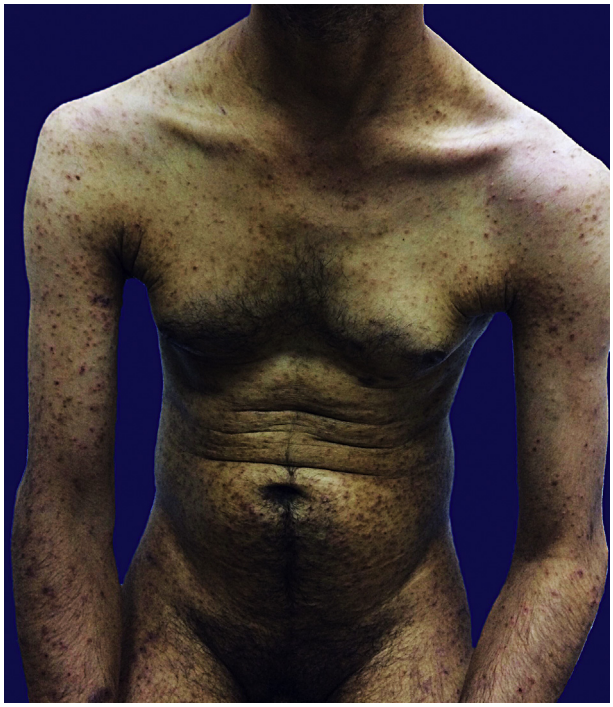

Fig. 9 Crusted scabies. (From Şişli Hamidiye Etfal Training and Research Hospital, Department of Dermatology).

corticosteroids, acitretin, or phototherapy, are safe options in HIV-infected individuals. Methotrexate and cyclosporine are associated with a high risk of opportunistic infections. Anti-tumor necrosis factor (TNF) treatments seem effective and well tolerated with a higher than 200 cells/μL absolute CD4 count; however, due to limited efficacy and safety data, some authors recommend limiting the use of anti-TNF agents to those resistant to standard therapeutic options. An increased risk for infections has been observed in patients with CD4 counts of less than 50 cells/μL, especially with anti-TNF agents. Ustekinumab apparently does not negatively affect CD4 count and HIV viral load. The safety and effectivity data on IL-17A and IL-23 inhibitors in HIV-infected individuals are still not enough.[22,23]

Seborrheic dermatitis

Seborrheic dermatitis (SD) (Figure 11) can be seen at all immunologic stages of HIV infection, with the overwhelming majority of patients experiencing SD during the course of the infection; nevertheless, the severity of SD is correlated with advanced immunosuppression. The morphology of HIV-related SD is usually identical to classic SD, but it differs in terms of chronicity and severity.[3,24]

Pruritic papular eruption

Pruritic papular eruption (PPE) is one of the most common cutaneous manifestations of HIV infection. Etiopathogenesis of the disease is unknown; however, a hypersensitivity reaction to arthropod bite has been suggested. It usually presents with pruritic, multiple, discrete, excoriated papular lesions and postinflammatory pigmentation on the trunk, extensor surfaces of the extremities, and face. The eruption may have periods of remission and exacerbation. The severity of the disease is inversely correlated with the absolute CD4 count. PPE may imitate eosinophilic folliculitis, staphylococcal folliculitis, demodicosis, photoallergic dermatitis, secondary syphilis, scabies, and papulonecrotic tuberculid.[25]

Eosinophilic folliculitis

Eosinophilic folliculitis (EF), Ofuji's disease (Figure 12), is a chronic, itchy disorder of unknown cause that waxes and wanes. It is associated with significant morbidity that is closely associated with an absolute CD4 count of less than 250 cells/μL. EF may also be seen in transplant recipients and patients with a hematologic disorder, possibly due to a follicular hypersensitivity reaction. EF is characterized by small reddish papulopustular lesions localized to the trunk, arms, shoulders, neck, and forehead. The differential diagnosis between PPE and EF may be very challenging because both may have similar clinical presentations. EF shows perifollicular infiltration of eosinophils, whereas PPE demonstrates perivascular mononuclear infiltration with eosinophils. EF may also imitate acneiform eruptions, suppurative folliculitis, pustular psoriasis, subcorneal pustular dermatosis, dermatitis herpetiformis, scabies, and photoallergic dermatitis.[26]

Atopic dermatitis

Atopic dermatitis (AD) may show exacerbation or recurrences during HIV infection. The stage of immunodeficiency does not affect the development of atopy.[26] The clinical presentation usually does not differ compared with HIV-negative individuals.

Xerosis

Xerosis is common in HIV infection and affects nearly 30% of HIV-infected individuals. The etiopathogenesis remains unclear; however, poor nutrition has been accused. HIV-related xerosis is characterized by diffuse dryness, hyperpigmentation, and crusting. Xerosis may imitate contact dermatitis, atopic dermatitis, mycosis fungoides, and psoriasis. Emollients containing a keratolytic are the mainstream treatment.[26]

Photosensitive dermatitis

Photosensitivity in the setting of HIV infection is a well-known phenomenon and affects about 5% of patients. The etiopathogenesis is unknown; however, dysfunction of the oxygen-free scavenging activity (which eliminates reactive oxygen species produced by ultraviolet radiation) has been accused. The severity of photosensitive disorders is correlated with the stage of immunosuppression and usually develops in patients with CD4 counts of less than 50 cells/μL.[27] Lichenoid eczematous dermatitis (LED) and chronic actinic dermatitis (LED) are well reported photosensitive diseases in HIV-infected individuals.[28] Lichenoid eczematous lesions are usually located on the

Table 1 The clinical manifestations and differential diagnosis of cutaneous infectious diseases in HIV infection

Infectious diseases	Clinical manifestations	Differential diagnoses
Viral infections		
Warts	Common warts in unusual sites with unusual severity	Verrucous carcinoma and squamous cell carcinoma
Epidermodysplasia verruciformis-like syndrome	Hypopigmented or pink macules, papules, plaques in sun-exposed sites, trunk, and extremities	Seborrheic keratosis, warts, and pityriasis versicolor
Herpes simplexital infection	Chronic nonhealing ulcerations and verrucous lesions	Pyoderma gangrenosum, atypical mycobacterial infection, deep fungal mycosis, verrucous carcinoma, condyloma lata, condyloma accuminata, pemphigus vegetans.
Herpes zosterital infection	Multidermatomal or disseminated involvement. Necrotic, hemorrhagic, verrucous, hyperkeratotic, ecthyma-like lesions	Bacterial infections, warts, pityriasis lichenoides, secondary syphilis, and vasculitis
Molluscum contagiosum	Generalized, chronic, recalcitrant, giant and verrucous lesions	Warts, basal cell carcinoma, keratoacanthoma, atypical mycobacterial infection, and deep fungal infection
Bacterial infections		
Mycobacterial infections	Hyperkeratotic plaques, ulcerations, abscesses	Deep fungal infection, sarcoidosis, leishmaniasis
Syphilis	Rapid progression to the advanced stage of the disease, atypical and extensive clinical manifestations	Other infectious causes of genital and extragenital ulceration, pityriasis rosea, psoriasis, drug eruptions, cutaneous T-cell lymphoma, lichen planus, contact dermatitis, atopic dermatitis, sarcoidosis
Bacillary angiomatosis	Countless papular, nodular lesions	Lobular capillary hemangioma, Kaposi's sarcoma, hemangiomas, cutaneous metastasis
Fungal infections		
Dermatophytosis	Chronic course with coalescent hyperpigmented plaques, proximal white onychomycosis	Contact dermatitis, mycosis fungoides, sarcoidosis
Candidosis	Chronic course and disseminated involvement	Aphthous stomatitis, lichen planus, leukoplakia, erythroplakia squamous cell carcinoma
Cutaneous cryptococcosis	A wide variety of lesions including papules, plaques, pustules, nodules, ulcerations	Molluscum contagiosum, pyogenic and nocardial abscess, cutaneous lymphoma, basal cell carcinoma, cutaneous tuberculosis, syphilis, cutaneous metastasis, histoplasmosis
Histoplasmosis	Diffuse erythema, papulopustular lesions, crusts, ulcerations, psoriasiform lesions	Molluscum contagiosum, pyogenic abscess, common warts, erythema nodosum, cutaneous metastasis, psoriasis
Parasitic infections		
Scabies	Crusted, hyperkeratotic lesions on erythematous base all over the body, including face	Ichthyosis, hyperkeratotic eczema, psoriasis, contact dermatitis, mycosis fungoides, and secondary syphilis

chest, nape, forearms, and dorsal surfaces of the hands.[26] LED can mimic lichenoid contact dermatitis and lichenoid drug eruption. CAD is characterized by thick confluent scaling plaques involving large areas. It may also involve sun-protected areas resulting in erythroderma and heals with prominent depigmentation.[27] CAD may imitate mycosis fungoides, contact dermatitis, and vitiligo. The histopathology usually shows a nonspecific spongiotic dermatitis pattern. Phototesting may be performed to confirm diagnosis.[29]

Table 2 summarizes the clinical findings and differential diagnosis of HIV-associated cutaneous inflammatory conditions.

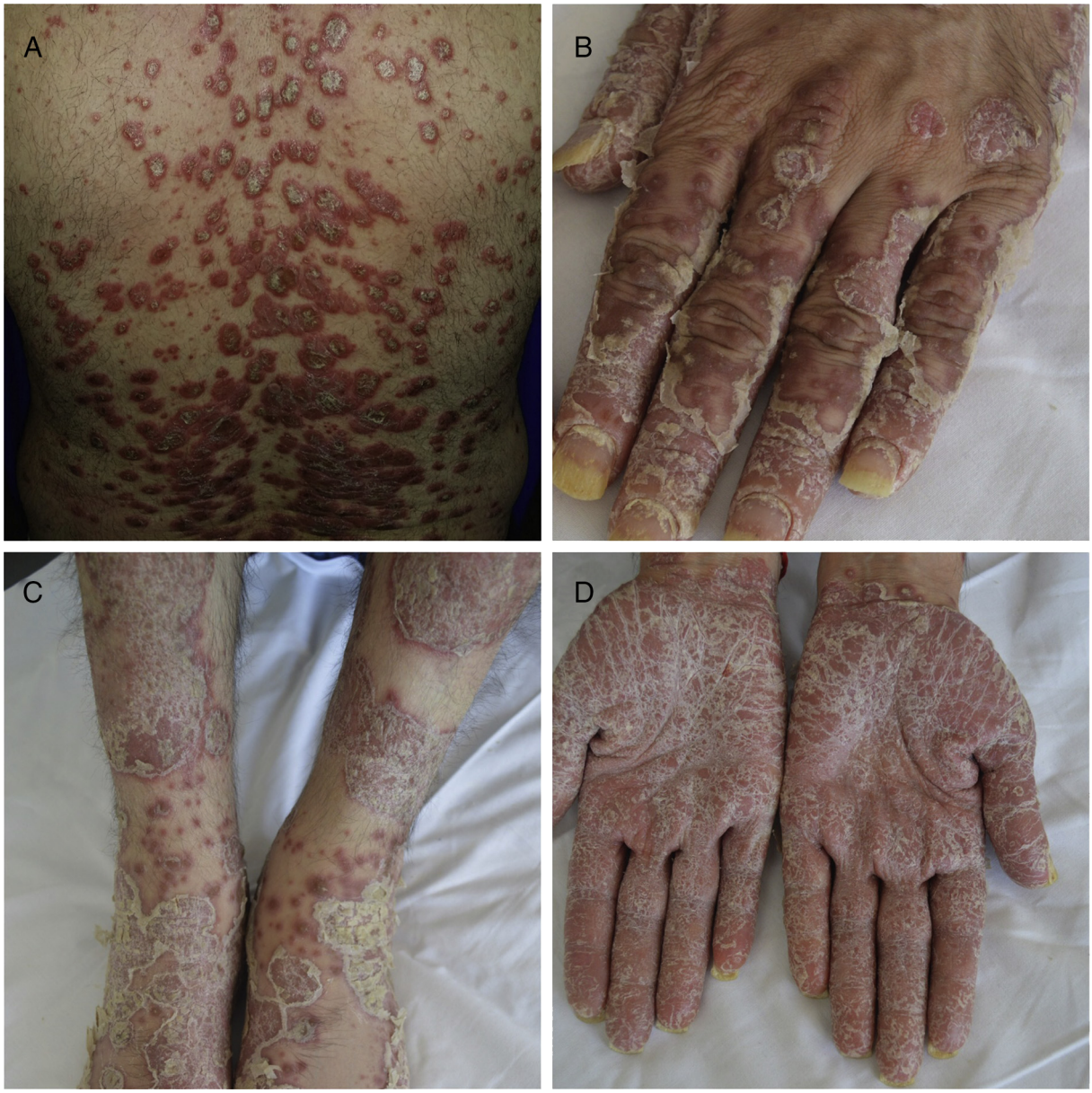

Fig. 10 Chronic plaque psoriasis localized on the back **(A)**, dorsal hand **(B)**, extensor surface of the lower extremity **(C)** and palms **(D)**. (From Istanbul Medeniyet University, Department of Dermatology).

Neoplastic conditions

Kaposi's sarcoma

Kaposi's sarcoma (KS) (Figures 13, 14) is a low-grade vascular tumor involving visceral organs and mucocutaneous surfaces caused by human herpesvirus (HHV)-8. Classic (sporadic) and epidemic (HIV-related) forms are the two main presentations of the entity.[30] The incidence of KS in HIV-infected individuals has decreased significantly with the use of HAART; nevertheless, HIV-infected individuals are still at an 800-fold increased risk of KS compared with the general population.[4] HIV-related KS usually reflects the advanced stage of the immunosuppression. The cutaneous manifestations in KS range from red or violaceous macules and patches to plaques and nodules. The lesions may grow and coalesce into large plaques. Cutaneous lesions are usually asymptomatic but may ulcerate and become secondarily infected.[3] In HIV-related KS, oral lesions are common and may cause dysphagia.[30] The mucocutaneous lesions may imitate bacillary angiomatosis, pyogenic granuloma, hemangioma, angiokeratoma, cutaneous lymphoma, and cutaneous metastasis.

Cutaneous lymphomas

Cutaneous involvement of non-Hodgkin lymphoma (NHL) and primary cutaneous B-cell lymphomas (PCBL) are rare in HIV-infected patients. HIV-related cutaneous B-cell lymphomas are usually reported to have atypical

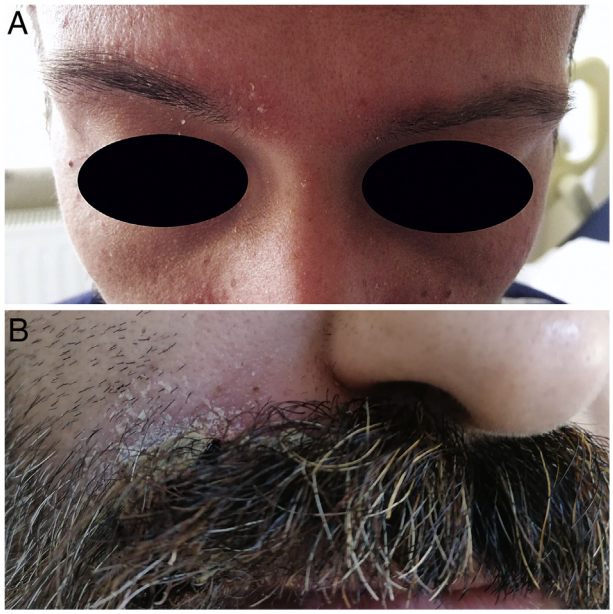

Fig. 11 Seborrheic dermatitis localized over the face **(A)** and upper lip **(B)**. (From Şişli Hamidiye Etfal Training and Research Hospital, Department of Dermatology).

morphology and severe clinical course. Diffuse large B-cell lymphomas (DLBCL) are the most common HIV-related form of cutaneous B-cell lymphomas. The typical presentation is a single rapidly growing deep skin nodule or plaque; however, the skin involvement may also include infiltrative macular lesions, papules, and ulcerations.[31,32] PCBL may imitate soft tissue sarcoma, squamous cell carcinoma, cutaneous metastasis, pyogenic abscess, atypical mycobacterial infections, and deep fungal infection. The diagnosis is based on histopathologic and immunohistochemical examination.[32]

There is another HIV-related lymphoproliferative disorder that closely imitates cutaneous T-cell lymphoma (CTCL). This disease is not a true lymphoma and is known as pseudo-CTCL or atypical cutaneous lymphoproliferative disorder. Pseudo-CTCL may have common clinical and histopathologic presentations with CTCL. Determining the clonality, T-cell receptor gene rearrangement should be performed for the differential diagnosis. Both CTCL and pseudo-CTCL may imitate a wide variety of cutaneous conditions, including drug eruptions, photodermatitis, atopic dermatitis, and psoriasis.[31]

Melanoma

The published data regarding whether HIV is associated with a higher incidence of melanoma are controversial.[33] Once melanoma has occurred in HIV-infected individuals, it shows a more aggressive behavior.[34] Cutaneous melanoma may mimic both benign and malignant conditions including nevi, dermatofibroma, seborrheic keratosis, nonmelanoma skin cancers, and metastatic carcinoma. HIV-related melanoma is usually associated with unfavorable treatment outcomes.[34]

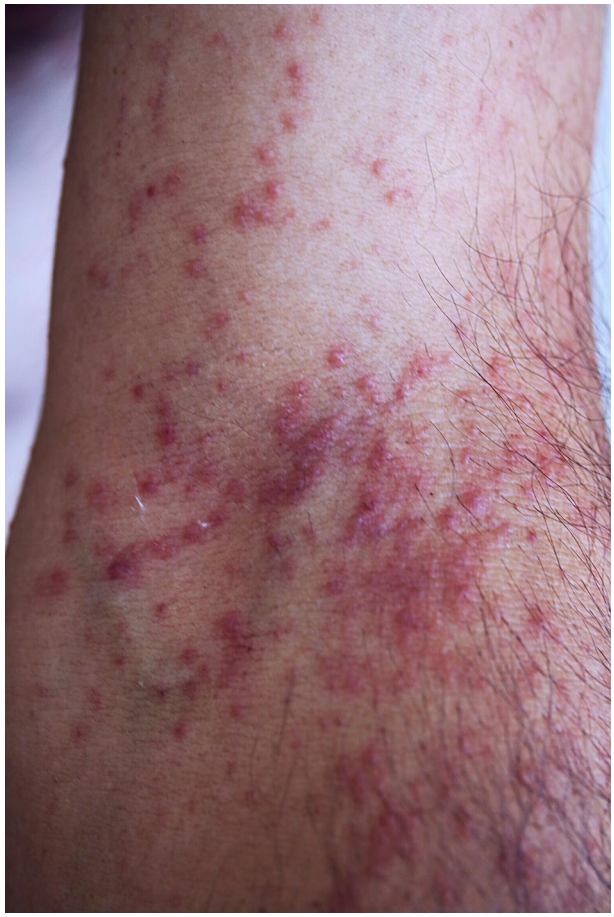

Fig. 12 Eosinophilic folliculitis localized on the medial malleolus. (From Istanbul Medeniyet Univesity, Department of Dermatology).

Nonmelanoma skin cancers

The role of HIV infection in nonmelanoma skin cancers (NMSC), including basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), is not well documented; however, recent studies suggest that HIV infection increases the risk of SCC in both sexes. The incidence of BCC is not increased, according to the HIV status.[35] The use of HAART is associated with a decreased risk of NMSC development. Lower CD4 counts seem to be associated with a higher incidence for SCC, but not for BCC. The clinical course, invasiveness, and differentiation of NMSC do not differ significantly by HIV status.[36]

Table 3 sums up the clinical clues and the differential diagnosis of HIV-related cutaneous neoplastic conditions.

HAART-associated adverse cutaneous reactions

HIV-infected individuals are much more susceptible to adverse cutaneous drug reactions (ACDR) than the general population. This increased risk is also correlated with the stage of immune dysfunction. Multiple drug intake, slow acetylator function, relative glutathione deficiency, a CD4 count of less than 200 cells/μL, latent cytomegalovirus, and Epstein-Barr virus infections are the main factors responsible for the higher risk of ACDR in HIV infection.[37]

Table 2 The clinical manifestations and differential diagnosis of cutaneous inflammatory diseases in HIV infection

Inflammatory diseases	Clinical manifestations	Differential diagnoses
Psoriasis	Much more severe course, erythroderma, rupoid lesions	Lamellar ichthyosis, erythrodermic drug eruption, mycosis fungoides, deep fungal infections, crusted scabies, and secondary syphilis
Seborrheic dermatitis	Back, axilla, and groin involvement	Inverse psoriasis, contact dermatitis, secondary syphilis, atopic dermatitis, drug eruptions, mycosis fungoides, and superficial fungal infections
Pruritic papular eruption	Itchy multiple, discrete, and excoriated papular lesions, postinflammatory pigmentation	Eosinophilic folliculitis, staphylococcal folliculitis, demodicosis, photoallergic dermatitis, secondary syphilis, scabies, and papulonecrotic tuberculid
Eosinophilic folliculitis	Millimetric reddish papulopustular lesions	Pruritic papular eruption, acneiform eruptions, suppurative folliculitis, pustular psoriasis, subcorneal pustular dermatosis, dermatitis herpetiformis, scabies, and photoallergic dermatitis
Atopic dermatitis	Poorly defined erythematous papulovesicular lesions, scale, and crusts	Contact dermatitis, mycosis fungoides, psoriasis, scabies, and drug eruptions
Xerosis	Diffuse dryness, hyperpigmentation, and crusting	Contact dermatitis, atopic dermatitis, mycosis fungoides, and psoriasis
Photosensitive dermatitis	Thick confluent scaling plaques involving large areas, prominent depigmentation, lichenoid eczematous lesions	Cutaneous T-cell lymphoma, lichenoid contact dermatitis, lichenoid drug eruption

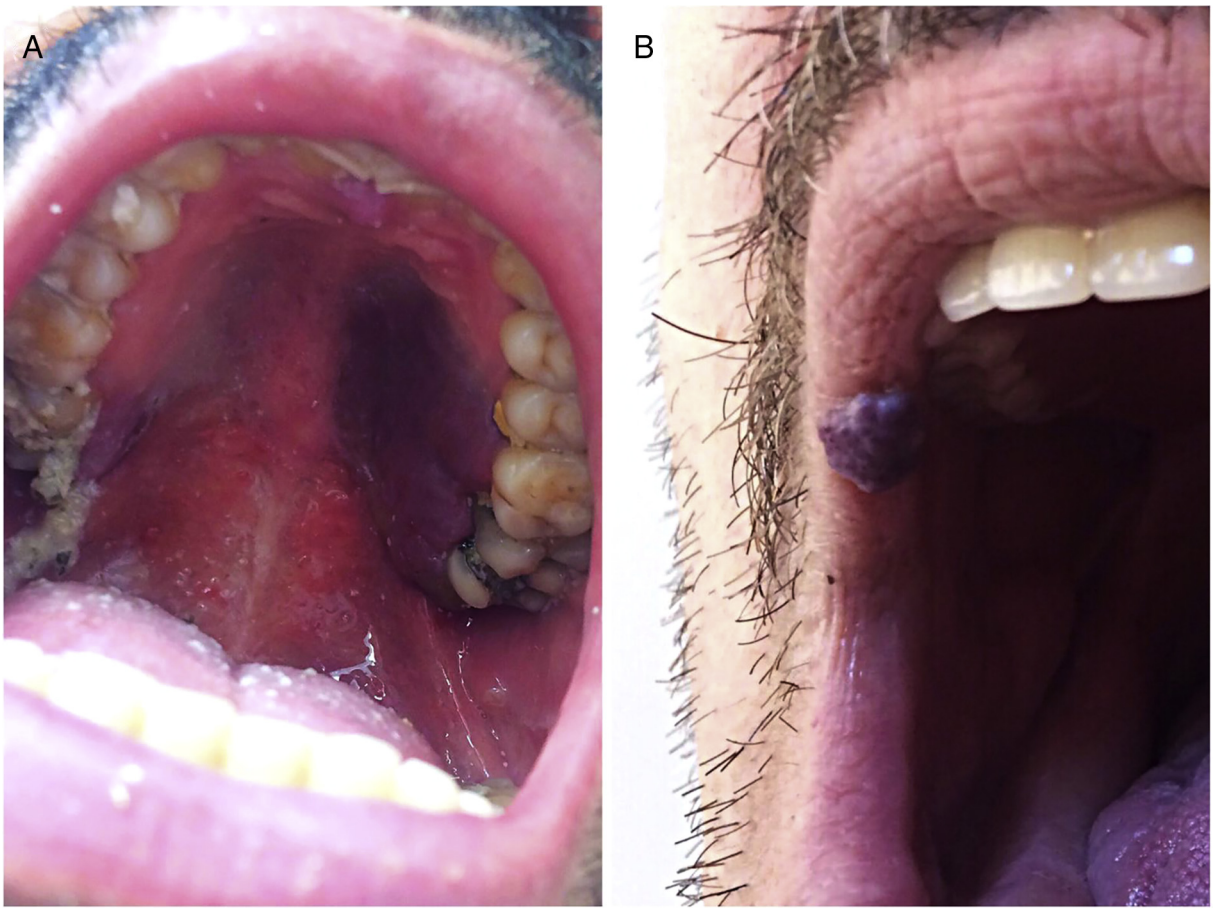

Fig. 13 Kaposi's sarcoma localized on the hard palate **(A)** and the upper lip **(B)**. (From Şişli Hamidiye Etfal Training and Research Hospital, Department of Dermatology).

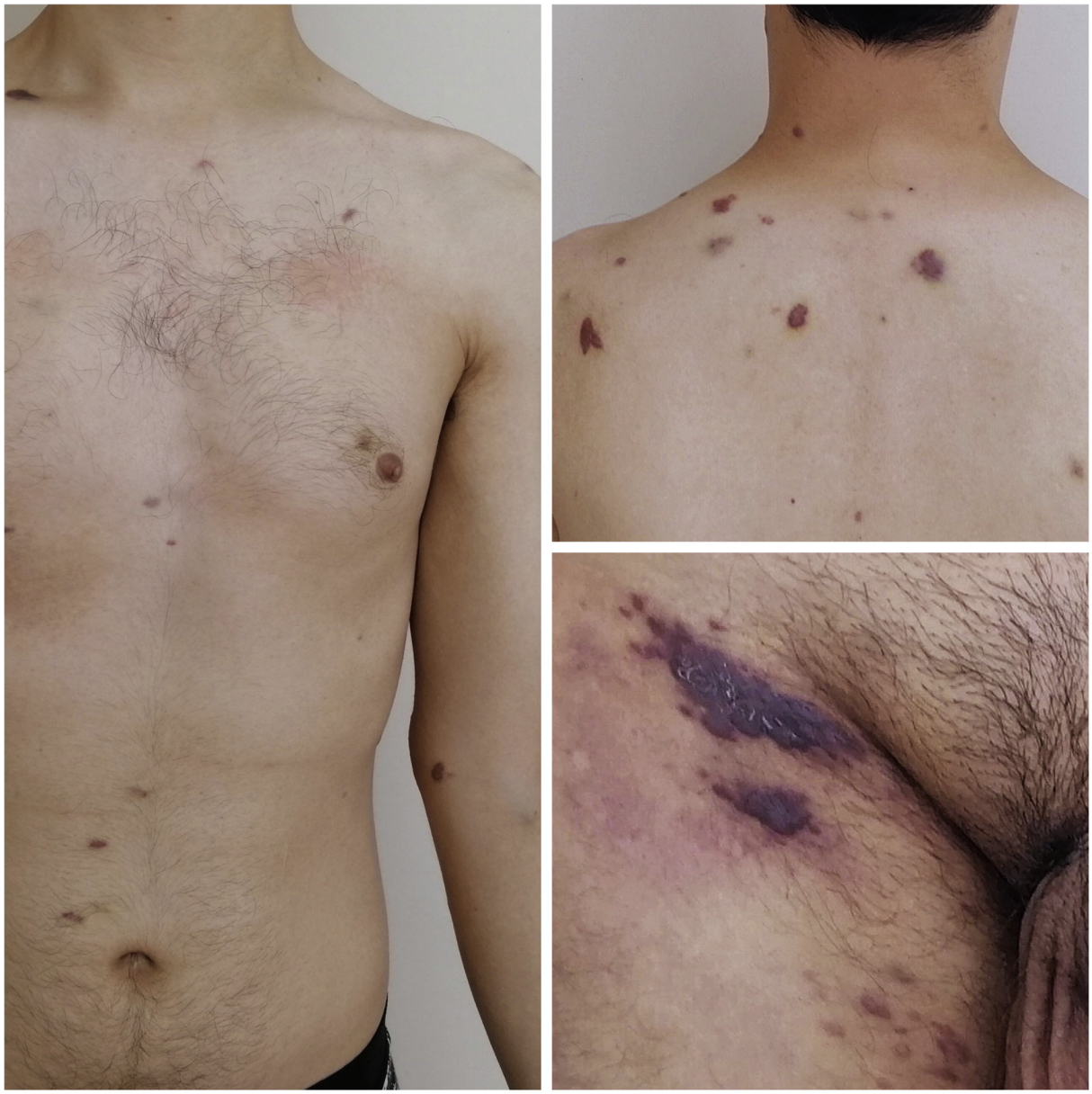

Fig. 14 Widespread nodular Kaposi's sarcoma. (From Şişli Hamidiye Etfal Training and Research Hospital, Department of Dermatology).

Table 3 The clinical manifestations and differential diagnosis of cutaneous neoplastic diseases in HIV infection

Neoplastic conditions	Clinical manifestations	Differential diagnoses
Kaposi's sarcoma	Mucocutaneous manifestations range from red or violaceous macules and patches to plaques and nodules; the plaques may grow and coalesce into large plaques	Bacillary angiomatosis, pyogenic granuloma, hemangioma, angiokeratoma, cutaneous lymphoma, and cutaneous metastasis
Cutaneous B-cell lymphoma	Single or multiple rapidly growing deep skin nodules, papules, plaques, and ulcerations	Soft tissue sarcoma, squamous cell carcinoma, cutaneous metastasis, pyogenic abscess, atypical mycobacterial infections, and deep fungal infection
Cutaneous T-cell lymphoma	Patches, plaques, nodules, erythroderma	Psoriasis, atopic dermatitis, contact dermatitis, pemphigus foliaceus, and drug eruptions
Melanoma	Much more aggressive clinical behavior	Nevi, dermatofibroma, seborrheic keratosis, nonmelanoma skin cancers, and metastatic carcinoma
Nonmelanoma skin cancers	Similar clinical course, invasiveness, and differentiation compared with negative HIV status.	

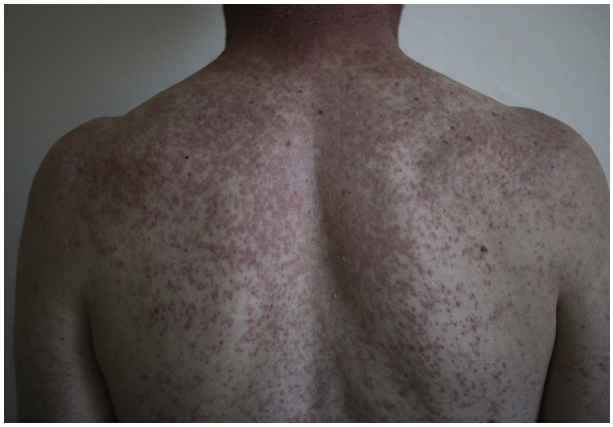

Fig. 15 Morbilliform drug eruption. (From Istanbul Medeniyet University, Department of Dermatology).

Morbilliform drug eruption (MDE) (Figure 15) is the most common form of ACDR. It typically begins 1 to 2 weeks after starting the therapy. Nonnucleoside reverse transcriptase inhibitors and protease inhibitors are the common causes.[38] MDE is characterized by an itchy, symmetrical, erythematous maculopapular eruption usually affecting the trunk. The face is typically spared. Fever, headache, muscle pain, and joint pain may also be seen. MDE may strongly imitate primary HIV infection. The presence of scattered dermal eosinophils may be a useful clue to differentiate MDE from primary HIV infection.[37] Urticaria, contact dermatitis, measles, and rubella, as well as secondary syphilis, are the other differential diagnoses.[3]

Antiretroviral therapy–related hypersensitivity syndrome is a life-threatening reaction that develops in the first 6 weeks of treatment. It is usually characterized by a widespread morbilliform eruption, fever, eosinophilia, atypical lymphocytes, elevated liver enzymes, and systemic involvement. Nevirapine, efavirenz, abacavir, amprenavir, and indinavir are the well-known causes. Immediate withdrawal of the offending drug is crucial.[37,39]

Erythema multiforme (EM) is characterized by erythematous target-shaped papules and vesiculobullous lesions usually involving distal extremities. EM may precede much more severe reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis, which are thought to reflect different severity spectrums of the same entity. Nonnucleoside reverse transcriptase inhibitors and protease inhibitors are the main causes. The differential diagnoses include febrile neutrophilic dermatoses, irritant contact dermatitis, autoimmune bullous dermatoses, and staphylococcal scalded skin syndrome.[18]

Table 4 summarizes the morphologic spectrum of ACDR and their differential diagnoses in HIV-infected individuals.

Conclusions

Skin diseases may be unique to patients with HIV infection or exacerbated by the accompanying immunologic deficiency. Although some conditions may not have an unusual morphology, others will be so augmented that the disease becomes a great imitator.

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Table 4 The morphological spectrum of ACDR in HIV-infected individuals

Drug reactions	Etiologic antiretroviral agents	Differential diagnoses
Morbilliform eruption	Delavirdine, etravirine, efavirenz, nevirapine, amprenavir, darunavir, atazanavir, and fosamprenavir[38]	Urticaria, contact dermatitis, measles, rubella, infectious mononucleosis, and secondary syphilis
Urticaria	Nevirapine and atazanavir[40]	Morbilliform drug eruption, contact dermatitis, urticarial vasculitis, and erythema multiforme
Erythema multiforme/Stevens-Johnson syndrome/toxic epidermal necrolysis	Amprenavir, fosamprenavir, efavirenz, and nevirapine[38]	Urticaria, acute febrile neutrophilic dermatosis, contact dermatitis, bullous pemphigoid, staphylococcal scalded skin syndrome, and paraneoplastic pemphigus
Fixed drug eruption	Nevirapine[40] and saquinavir[41]	Bullous insect reactions, irritant contact dermatitis, and localized bullous pemphigoid
Lichenoid eruption	Tenofovir,[42] efavirenz,[43] and zidovudine[44]	Liken planus, lichenoid contact dermatitis, psoriasis, secondary syphilis, and graft versus host disease
Mucocutaneous pigmentation and melanonychia	Zidovudine[45]	Subungual melanoma, subungual nevus, Laugier-Hunziker syndrome, and Addison disease
Lipodystrophy	Nucleoside reverse transcriptase inhibitors and protease inhibitors[46] (especially zidovudine and stavudine)	Hereditary lipodystrophy syndrome, insulin associated lipodystrophy, trauma induced lipodystrophy, panniculitis, and idiopathic localized dystrophy

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