การพบผื่นที่มีลักษณะไม่ตรงไปตรงมาของโรคลูปัสที่ผิวหนังในผู้ป่วยติดเชื้อเอชไอวี: รายงานผู้ป่วย

Atypical Manifestation of Cutaneous Lupus Erythematosus in Human Immunodeficiency Virus Infection Patient: A Case Report

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Abstract

Cutaneous lupus erythematosus (CLE) and Human Immunodeficiency Virus (HIV) infection are caused by the opposite effect of the immune response, increased immune activity in CLE, and decreased activity in HIV infection. CLE is an immune complex-mediated autoimmune disorder that interacts with multifactorial causes. CLE has three different presentation types: acute, subacute, and chronic; each type has a typical and atypical presentation, while HIV infection is an immunodeficiency disorder caused by a virus that affects T-lymphocyte CD4+ cells. We report a case of an atypical rash of CLE in a male with HIV infection. The pathogenetic implications of this coexistence of CLE and HIV are discussed. Furthermore, the treatment is very challenging.

Keywords : Cutaneous lupus erythematosus, Atypical manifestration, Human Immunodeficiency Virus, coexistence, HIV infection

บทคัดย่อ

โรคลูปัสที่ผิวหนัง และการติดเชื้อเอชไอวีนั้นมีการตอบสนองของระบบภูมิคุ้มกันในร่างกายที่แตกต่างกัน โรคลูปัสผิวหนังจะมีระบบภูมิคุ้มกันที่เพิ่มขึ้น และการติดเชื้อเอชไอวีจะทำให้ภูมิคุ้มกันลดลง โดยพบว่าโรคลูปัสที่ผิวหนังมีสาเหตุจาก immune complex-mediated autoimmune disorder ซึ่งก็คือการที่ระบบภูมิคุ้มกันในร่างกายทำงานมากเกินไป โดยโรคลูปัสที่ผิวหนังสามารถแบ่งได้เป็น 3 ประเภท คือ โรคลูปัสผิวหนังชนิดเฉียบพลัน กึ่งเฉียบพลัน และเรื้อรัง ซึ่งแต่ละประเภทจะมีลักษณะทางผิวหนังที่แตกต่างกัน และแบ่งออกเป็นผื่นที่พบบ่อย และผื่นที่ไม่ตรงไปตรงมา ส่วนการติดเชื้อเอชไอวีนั้นถือว่าเป็น immunodeficiency disorder คือโรคที่ทำให้ระบบภูมิคุ้มกันของร่างกายลดลงจากการติดเชื้อไวรัส ซึ่งจะไปทำลายเม็ดเลือดขาวชนิด T-lymphocyte CD4+ บทความนี้จะรายงานกรณีของผู้ป่วยเพศชาย ซึ่งมีโรคประจำตัวคือเอชไอวี แต่พบลักษณะของโรคลูปัสที่ผิวหนังร่วมด้วย ซึ่งการรักษาผู้ป่วยรายนี้มีความท้าทายมาก

คำสำคัญ: โรคลูปัสที่ผิวหนัง, ผื่นที่ไม่ตรงไปตรงมา, เอชไอวี, การพบร่วมกัน, การติดเชื้อเอชไอวี

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Introduction

The coexisting skin lesion of cutaneous lupus erythematosus (CLE) and human immunodeficiency virus (HIV) infection are rarely reported worldwide, especially in males. CLE is an immune complex-mediated autoimmune disorder involving the skin and adnexal structures. The increasing immune complex of self-antigens causes this disease.[1,2] That result from the interaction between genetic, epigenetic, immunoregulatory, ethnic, hormonal, and environmental factor.[3]

Introduction

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The first is a genetic factor in Systemic lupus erythematosus (SLE) that is associated with single gene deficiency, such as the complement components C1q that are involved with the elimination of necrosis material, and C4, concerned with the elimination of self-reactive-B cells, together with the combination of many genes.[4] The second is epigenetics, DNA methylation, and histone modification are the main factor. In addition some gene (ITGAL, CD40LG, CD70 and PPP2CA) involved with pathogenesis of LE too.[4] The third is immunoregulatory, dysregulation of T cell and B cell; abnormal signaling pathway and imbalance of T cell.[5] And the fourth is ethnic; the prevalence of SLE in African American women is higher than in Hispanics and Asian women; Caucasian women are the least prevalent.[6] The fifth is hormonal; SLE is presented in females more than males because of X-linked genetic factors. XIST, the long non-coding RNA in X chromosome.[6,7]

The clinical of CLE is divided into three types, acute, subacute, and chronic; each type has a different clinical presentation.[8] In acute cutaneous LE or ACLE, the typical lesion is Butterfly erythema (Tab.1). An atypical presentation is generalized ACLE, and bullous LE (Tab.1), both types are present at photodistributed areas. Subacute cutaneous LE, or SCLE, had two different forms of typical manifestation located on the photodistributed area, annular form, and papulosquamous form (Tab.1).[8] An atypical form divided into three types, Erythrodermic LE, Lupus erythematosus gyrates repens, and erythema annulare centrifugum like LE (Tab.1).[8] Furthermore, the last is chronic cutaneous LE or CCLE; they had two typical presentations Localized discoid lupus erythematosus (LDLE), and diffuse discoid lupus erythematosus (DDLE) (Tab.1). An atypical form is divided into three types: hypertrophic discoid lupus erythematosus, lupus comedonicus, and lupus mastitis (Tab.1).[8] Moreover, the last is another form of atypical CLE. They are divided into five types.[8] First is papulonodular mucinosis, that 80% of cases associated with SLE. And second is linear LE: a scarce variant, found in children, the lesion present along blaschko lines on the face.[8] Third is monogenic lupus erythematosus (MLE): a rare variant of LE caused by a single gene mutation that appears within five years of life with systemic symptoms.[8] The fourth is TEN-like-LE: a scarce and severe form of ACLE associated with a drug reaction, and the last is EEM-like LE: a very rare and severe

Tab.1 Typical and atypical manifestations of CLE[8]

TYPE OF CLE	TYPICAL MANIFESTRATION	ATYPICAL MANIFESTRATION
ACUTE CUTANEOUS LE (ACLE)	Butterfly erythema - The erythematous rash located at the malar area and cures without a scar	Generalized ACLE - Generalized maculopapular to an urticarial rash at photodisitricution areas and healed without a scar. Bullous LE - Disseminated vesicles or bullae that turn to eroded patches with crusted at photodistributed areas.

Tab.1 Typical and atypical manifestations of CLE[8] (ต่อ)

TYPE OF CLE	TYPICAL MANIFESTRATION	ATYPICAL MANIFESTRATION
SUBACUTET CUTANEOUS LE (SCLE)	Annular form - Symmetrical recurrent erythematous rash in an annular shape at photodistributed areas. Papulosquamous form - Symmetrical erythematous scaly plaques at photodistributed areas.	Erythrodermic LE - Generalized exfoliative erythroderma at photodistributed areas. Lupus erythematosus gyrates repens - Chronic recurrent gyrate erythema at photodistributed areas. Erythema annulare centrifugum like LE - Annular erythematous plaques with trailing scale at photodistributed areas.
CHRONIC CUTANEOUS LE (CCLE)	Localized discoid lupus erythematosus (LDLE) - The most common variant of CCLE-Erythematous hyperkeratotic plaques with dyspigmentation and scarring , localized on the head and neck areas. Diffuse discoid lupus erythematosus (DDLE) - The clinical presentation similar as LDLE but disseminated below the neck.	Hypertrophic discoid lupus erythematosus - A very hyperkeratotic lesion with congestive margin and central atrophy on the face, and extensor surface of the limbs. Lupus comedonicus - Erythematosus infiltrative plaque with open comedones. Lupus mastitis - Lupus profundus on the breast
	Papulonodular mucinosis - Asymmetrical skin-color papules and nodules located on the trunk and upper limbs. - Associated with SLE 80%. linear LE - A scarce variant. - Primarily present in children, the lesion present along blaschko lines on the face. Monogenic lupus erythematosus (MLE) - A rare variant of LE caused by a single gene mutation that appears within five years of life with systemic symptoms. TEN-like-LE - a scarce and severe form of ACLE. - Associated with a drug reaction. EEM-like LE - A very rare and severe form of ACLE. - Associated with drug reaction and herpes virus.	

Case Report

A 33-year-old male with no known underlying diseases, presented with two bizarre shaped, sharp-bordered, erythematous atrophic patches on the right medial cheek-nose-upper lip area and the left upper eyelid-lower forehead area with loss of some of his mustache and the left eyebrow for one month (Fig. 1). The pinprick sensation was normal. He did not have any oral ulcer, genital ulcer or rash on palms and soles. Laboratory investigations revealed the presence of HIV 1 antibodies in the serum with CD4 count 45 cells/mm.^{3}, negative of VDRL and TPHA, serum complete blood count, creatinine clearance and urinalysis are normal. The microscopic examination of the right medial cheek skin biopsy (Fig. 2) revealed some scale crust with hyperkeratosis and parakeratosis at the stratum corneum. Basal vacuolization was presented in the stratum basale. In the dermis, there were superficial and deep perivascular and peri-adnexal infiltrations of lymphocytes and plasma cells. Immunohistochemical study showed CD 123+ plasmacytoid dendritic cells in a cluster. The histopathology diagnosis compatible with cutaneous lupus erythematosus. Through waiting for the biopsy result, he was admitted to the local hospital due to sepsis with extensive genital-perianal ulceration. The Tzanck smear from the ulcer showed positive for multinucleated giant cells. Despite receiving intravenous acyclovir, he died three days after hospitalization.

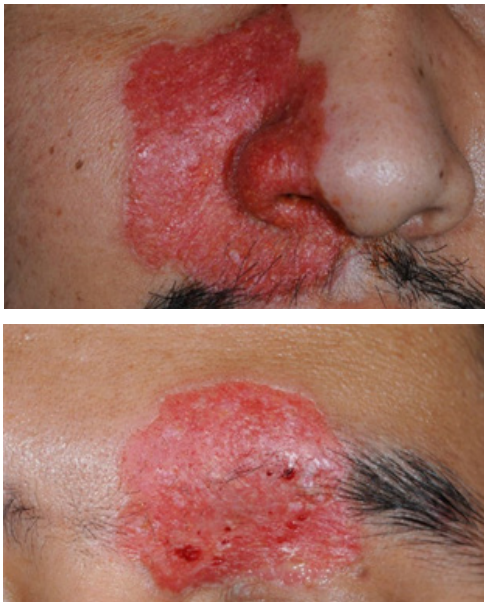

Fig. 1 Erythematous atrophic patches on the medial and the lower forehead areas with loss of some mustache and the left eyebrow.

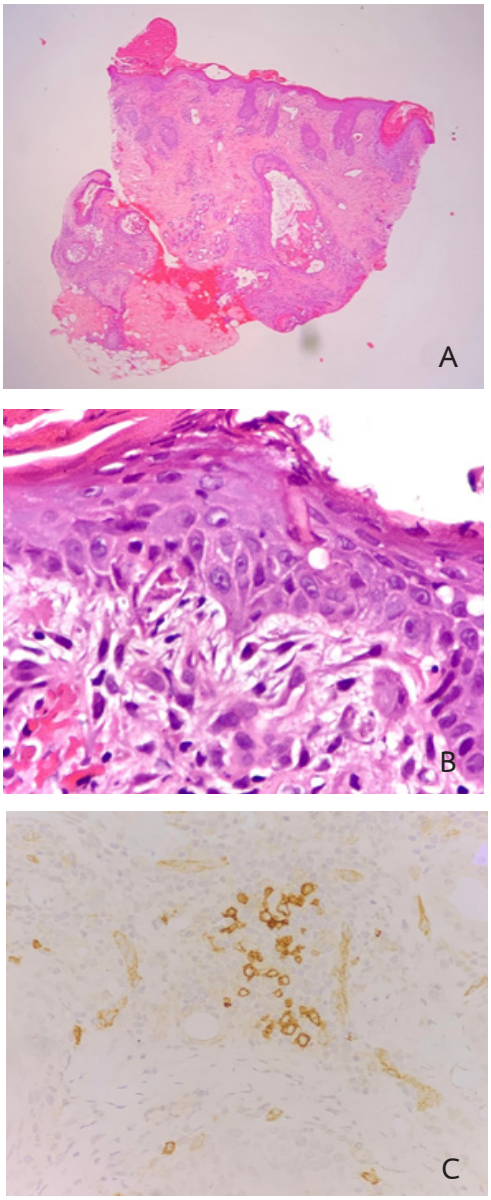

Fig. 2 A) Biopsy from the cheek demonstrates superficial and deep perivascular and peri- adnexal infiltration. B) High power view demonstrates basal vacuolization with perivascular infiltration with lymphoplasma cells. C) CD123 immunohistochemistry showing marked CD123 predominant at plasmacytoid dendritic cells in clusters. (A and B, Hematoxylin-eosin stain; original magnifications: A,x400; B,x600.), (C, CD 123 immunohistochemistry; original magnification: C, x600.)

Discussion

CLE and HIV infection affected T-cell lymphocytes; however, the pathogenesis differ.[12] CLE caused by autoimmunity that increases the production of immune complexes and pro-inflammatory cytokines. On the other hand, HIV infection is caused by a viral infection that attacks the immune system, leading to immunodeficiency.[1,11,13] These manifestations can be found together, although they have the opposite effect on the immune system.[14,15]

In the case-based review of Carugati M. et al., they reported two cases of systemic lupus erythematosus (SLE) combined with HIV-infected patients.[14] They suggested three relevant issues of SLE and HIV infection.[14] First, for their pathogenetic interactions, they said that autoimmune disease could occur despite the loss of immunocompetence caused by HIV infection. HIV infection affects regulatory T-cells that maintain peripheral self-tolerance and prevent the development of autoimmunity.[14] Second, the multifaceted clinical manifestation of SLE is mentioned, while the third issue is the therapeutic challenge posed by the coexistence of SLE and HIV.[14] Similarly, Goddard GZ. et al. said that infection could trigger immune activation and progress to autoimmune disease, but in HIV-infected patients, this disease causes the immunosuppressive effect, so clinical signs of SLE should be better due to the inhibition of autoimmune development.[12] In the case-based review of Calza L. et al., they reported a case of SLE and a case of discoid lupus erythematosus (DLE) in HIV-infected patients after receiving the antiretroviral drugs.[15] The first case was a middle-aged woman with HIV infection who received antiretroviral drugs (ARV) for two years. She presented with malar rash; her CD4+ count was 291 cells/mm^3. Later she was diagnosed with SLE.[15] The second case was a middle-aged female with HIV infection who received ARV for 16 months and presented with maculopapular rashes on her face. The CD4+ count was 572 cells/mm^3, later she was diagnosed with DLE by histopathology.[16] As in the previous case report of Calza L. et al., Chamberlain AJ. et al. reported the case of a patient with tumid lupus erythematosus due to the manifestation of immune restoration.[16] They reported the case of 42-year-old white man who had HIV infection. His CD4 count before starting ARV was $50x10^6L^{-1}$. After using ARV for ten months, he developed a facial rash. A dermatological examination revealed edematous erythematous papules and plaque that affected the forehead, cheeks, and ear lobes. Firstly, he was treated as a drug eruption, but his rash did not improve. Later, his rash improved with decreased CD4 count, so the doctor suspected he had an autoimmune disease. The laboratory results were all negative. He was diagnosed with tumid lupus erythematosus by histology.[16] Liao et al. reported a case similar to our patient from China. A Chinese man presented with edema, hematuria, and fever. He has been diagnosed with SLE and SLE lupus nephritis due to positive ANA and dsDNA with decreased C3 and C4 levels and increased serum creatinine with proteinuria and hematuria. He received prednisolone and cyclosporine for his condition. Later he was admitted to the hospital due to cold, facial edema, and gross hematuria. His routine workup showed HIV electrochemiluminescence immunoassay was positive and CD4 count was 138 cells/mm^3, so he was diagnosed with HIV infection.[17] Liao et al. reported another 76 cases reported of concomitant HIV infection and SLE from the literature review. Thirty-four cases had HIV infection followed by SLE, thirteen cases were pediatric patients, and the rest were adult, Two with CD4 more than 500 cells/mm^3, but CD4 was not mentioned in 4 cases, and the rest with CD4 less than 500 cells/mm^3. And they found a patient who was diagnosed with HIV infection and SLE in the same visit for 10 cases; three were not received ARV, one patient died from meningitis, two patients developed lupus flare, one patient had flare disease after receiving ARV, and the rest were inactive or improved SLE after receiving ARV.[17]

These examples from the literature showed that SLE, DLE, or tumid lupus erythematosus could

be presented in HIV-infected patients. HIV infection can be one of the risk factors of autoimmune disease; however, from the opposite pathophysiology of the immune system in these two diseases, the patient who has severe HIV infection should experience inhibited SLE or DLE symptoms due to the decrease of T-cell lymphocytes and the symptoms of SLE or DLE should flare when the patient's immune system is better, known as immune restoration.[11,13-15]

In addition, our patient had a bizarre shape with a sharp-bordered erythematous atrophic patches on the face, including the nasolabial fold; this type of lesion is incompatible with the typical presentation of CLE and another form of atypical CLE too. According to our knowledge form of the lesion (bizarre shape) is a pretty atypical presentation of a lupus lesion, but from histology, it is compatible with cutaneous lupus erythematosus.

In conclusion, the coexistence of CLE and HIV infection can be found in the male. Treating such patients can become a real challenge as CLE is an autoimmune disorder leading to atrophic scars and scarring alopecia. Treatment of CLE with systemic immunosuppressive agents can disturb immunity, leading to severe life-threatening infections.

In most cases, from literature review found that treatment with an HIV infection regimen alongside with SLE or CLE regimen was a good result.[12,14-16]

References

1. Kalden JR, Winkler TH, Herrmann M, Krapf F. Pathogenesis of SLE: immunopathology in man. Rheumatol Int. 1991;11(3):95-100.
2. Kiriakidou M, Ching CL. Systemic Lupus Erythematosus. Ann Intern Med. 2020;172(11):ITC81-96.
3. Pyfrom S, Paneru B, Knox JJ, Cancro MP, Posso S, Buckner JH, et al. The dynamic epigenetic regulation of the inactive X chromosome in heathy human B cell is dysregulated in lupus patients. Proc Natl Acad Sci USA. 2021;118(24):e2024624118.
4. Tsokos GC. Mechanism of disease systemic lupus erythematosus. N Engl j Med. 2011;365:2110-21.
5. Pan L, Lu M-P, Wang J-H, Xu M, Yang S-R. Immunological pathogenesis and treatment of systemic lupus erythematosus. World J Pediatr.2020;16(1):19-30.
6. Yu B, Qi Y, Li R, Shi Q, Satpathy AT, Chang HY. B cell-specific XIST complex enforces X-inactivation and restrains atypical B cells. Cell. 202;184(7):1790-180.e17.
7. Zucchi D, Elefante E, Schiliro D, Signorini V, Tretin F, Bortoluzzi A, et al. One year in review 2022: systemic lupus erythematosus. Clin Exp Rheumatol. 2022;40(1):4-14.
8. Herzum A, Gasparini G, Cozzani E, Burlando M, Parodi A, Atypical and rare form of cutaneous lupus erythematosus: The importance of the diagnosis for the best management of patients. Dermatology.2021;238(2):195-204.
9. Gallo RC, Garzino-Demo A, DeVICO AL. HIV infection and pathogenesis: What About Chemokines? J Clin Immunol. 1999;19(5):293-9.
10. Yen YF, Chuang PH, Jen IA, Chen M, Lan YC, et al. Incidence of autoimmune disease in a nationwide HIV/AIDS patient cohort in Taiwan, 2000-2012. Ann Rheum Dis. 2017;76(4):661-5.
11. Fox RA, Isenberg DA. Human immunodeficiency virus infection in systemic lupus erythematosus. Arthritis Rheum. 1997;40(6):1168-72.
12. Goddard GZ, Shoenfeld Y. HIV and autoimmunity. Autoimmun Rev. 2002;1(6):329-37.
13. Abbot IJ, Chand CC, Skinner MJ, Street A, Perry G, et al. Development and management of systemic lupus erythematosus in an HIV-infected man with hepatitis C and B co-infection following interferon therapy: a case report. J Med Case Rep. 2009;3:7289.
14. Carugati M, Franzetti M, Torre A, Giorgi R, Genderini A, et al. Systemic lupus erythematosus and HIV infection; a whimsical relationship. Reports of two cases and review of the literature. Clin Rheuma-

tol. 2013;32(9):1399-405.

15. Calza L, Manfredi R, Colangeli V, D'Antuono A, et al. Systemic and discoid lupus erythematosus in HIV-infection patients treated with highly active antiretroviral therapy. Int J STD AIDS. 2003;14(5): 356-9.
16. Chamberlain AJ, Hollowood K, Turner RJ, Byren I. Tumid lupus erythematosus occurring following highly active antiretroviral therapy for HIV infection: A manifestation of immune restoration. J Am Dermatol. 2004;51:S161-5.
17. Liao HY, Tao CM, Su J. Concomitant systemic lupus erythematosus and HIV infection: A rare case report and literature review. Medicine. 2017;96(51): e9337.