—Case Reports—

Lupus Erythematosus Tumidus with Pseudolymphomatous Infiltrates: A Case Report

Yuki Umeda[1], Keigo Ito[2], Shinichi Ansai[2], Toshihiko Hoashi[3], Hidehisa Saeki[3] and Naoko Kanda[1]

[1]Department of Dermatology, Nippon Medical School Chiba Hokusoh Hospital, Chiba, Japan
[2]Department of Dermatology, Nippon Medical School Musashi Kosugi Hospital, Kanagawa, Japan
[3]Department of Dermatology, Nippon Medical School, Tokyo, Japan

A 39-year-old Japanese woman presented with a pruritic infiltrated erythematous plaque on the right cheek. Histopathologic analysis of the erythema showed dermal edema, separation of collagen bundles, and nodular perivascular and periadnexal infiltration of lymphocytes in the whole dermis, without epidermal changes. Alcian blue staining intensity was elevated between the collagen bundles, indicating dermal mucinosis. The nodular infiltrates consisted of CD3+ T cell clusters and CD20+ B cell clusters (ratio, approximately 3:1) and included numerous CD123+ cells, indicative of plasmacytoid dendritic cells. Blood analysis revealed serum antinuclear antibody at a titer of 1:160 (homogeneous, speckled pattern). Lupus erythematosus tumidus with pseudolymphomatous infiltrates was diagnosed. Hydroxychloroquine treatment partially improved symptoms; however, the addition of prednisolone was required for complete resolution. Lupus erythematosus tumidus is sometimes accompanied by pseudolymphomatous infiltrates. Dermal mucinosis and the presence of numerous plasmacytoid dendritic cells are useful in differentiating lupus erythematosus tumidus from pseudolymphoma.
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Key words: lupus erythematosus tumidus, pseudolymphoma, mucinosis, plasmacytoid dendritic cell

Introduction

Lupus erythematosus tumidus (LET) is a cutaneous LE characterized by infiltrated erythema occurring mainly on sun-exposed regions of the skin and histopathological findings of dermal mucinosis[1,2]. Exposure to ultraviolet rays is believed to be a triggering factor for LET. There are very few reports of LET cases in Japan[3]. Pseudolymphoma manifests as erythematosus papules, nodules, or plaques on the face or arm and is characterized by a reactive polyclonal benign lymphoproliferative process comprising B cells, T cells, or both[4]. Pseudolymphoma may be caused by microbial, physical, or chemical factors; *Borrelia burgdorferi* infection; insect bites; tattoos; or drugs.

Histopathologically, LET is accompanied by dense perivascular and periadnexal infiltration of lymphocytes, which sometimes mimics pseudolymphoma[5]. Herein we describe a case of LET with pseudolymphomatous infiltrates in a Japanese woman and discuss the pathogenesis of this condition.

Case Report

A 39-year-old Japanese woman with no reported history of medication use visited a dermatological clinic for evaluation of erythema on her right cheek. She was prescribed topical corticosteroids and oral antihistamine H1 receptor antagonists for 1.5 months; however, the erythema grew larger. On a later visit to another clinic, she was prescribed topical tacrolimus and oral doxycycline 100 mg/day for 4.5 months, with no effect. She was then referred to our department.

On presentation, there was a pruritic infiltrated erythe-

Correspondence to Naoko Kanda, MD, PhD, Department of Dermatology, Nippon Medical School Chiba Hokusoh Hospital, 1715 Kamagari, Inzai, Chiba 270–1694, Japan
E-mail: n-kanda@nms.ac.jp
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matous plaque on the right cheek (**Fig. 1**). Blood analyses revealed serum antinuclear antibody at a titer of 1:160 (homogeneous, speckled pattern). Other specific autoantibodies and anti-*Borrelia burgdorferi* antibody were absent. Moreover, no hypocomplementemia or abnormalities in blood cell count were observed. The patient denied photosensitivity; however, her right cheek was exposed to solar radiation during daily driving. A provocative phototest was not performed. Histopathological examination of the erythema showed dermal edema and separation of collagen bundles. In addition, dense nodular perivascular and periadnexal infiltration of lymphocytes mixed with histiocytes lacking atypical features were observed in the superficial and deep dermis (**Fig. 2a, b**). No alteration of the epidermis or dermo-epidermal interface was seen. The intensity of Alcian blue staining was elevated between collagen bundles in the dermis, indicating mucin deposition (**Fig. 2c**). The infiltrates were composed of CD3+ cell clusters (**Fig. 3a**) and CD20+ cell clusters (**Fig. 3b**) (approximate ratio, 3:1) and included numerous CD123+ cells, indicative of plasmacytoid dendritic cells (pDCs) (**Fig. 3c, d**). Immunoglobulin λ-chain and κ-chain were present in very few cells, and no light chain restriction was observed. None of the infiltrate samples tested positive for CD30. On the basis of these clinicopathological findings, LET with pseudolymphomatous infiltrates was diagnosed. The patient was treated with hydroxychloroquine (HCQ) 200 mg/400 mg every other day and was advised to use sunscreen lotions with high protection against UVA and UVB. At 7 weeks, her erythema was slightly flattened; however, infiltrate remained and prednisolone 15 mg/day was therefore added. Three weeks later, infiltration was reduced and color tone was faint; however, the eruption was still present. Six weeks later, the prednisolone dose was increased to 25 mg/day, which resulted in complete resolution of the eruption. The prednisolone dose was later gradually tapered. At 22 weeks after the start of therapy, treatment with HCQ 200 mg/400 mg every other day and prednisolone 17.5 mg/day was continued, without recurrence.

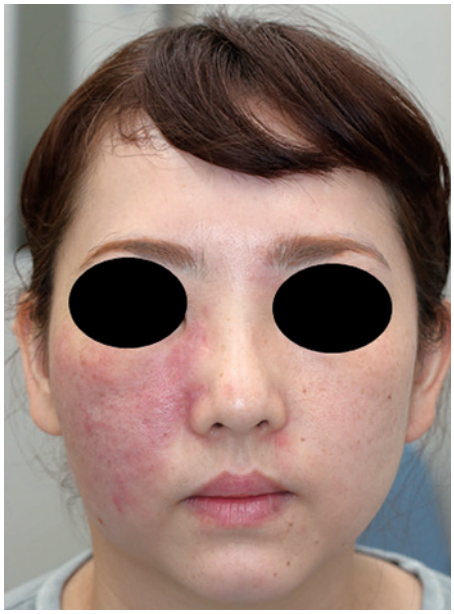

Fig. 1 The patient presented with an infiltrated erythematous plaque on the right cheek.

Discussion

The present patient's skin lesion was histopathologically characterized by dermal mucinosis associated with pseudolymphomatous infiltrates. Pereira et al. described the histopathological spectrum of pseudolymphomatous infiltrates in cutaneous LE, including LET[5], and reported that clues to the histopathological diagnosis of cutaneous

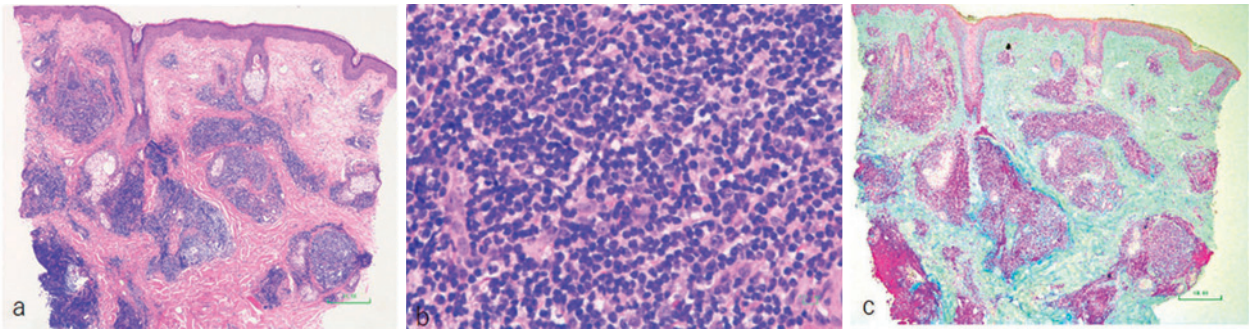

Fig. 2 (a) Histopathological examination by hematoxylin and eosin staining showed dermal edema, separation of collagen bundles, and dense nodular infiltration of lymphocytes surrounding the vessels and appendages in the whole dermis. (b) The infiltrating cells were mainly lymphocytes mixed with histiocytes, without atypical features. (c) Alcian blue staining intensity was elevated between collagen bundles in the dermis. Original magnification: (a, c) ×40 and (b) ×400.

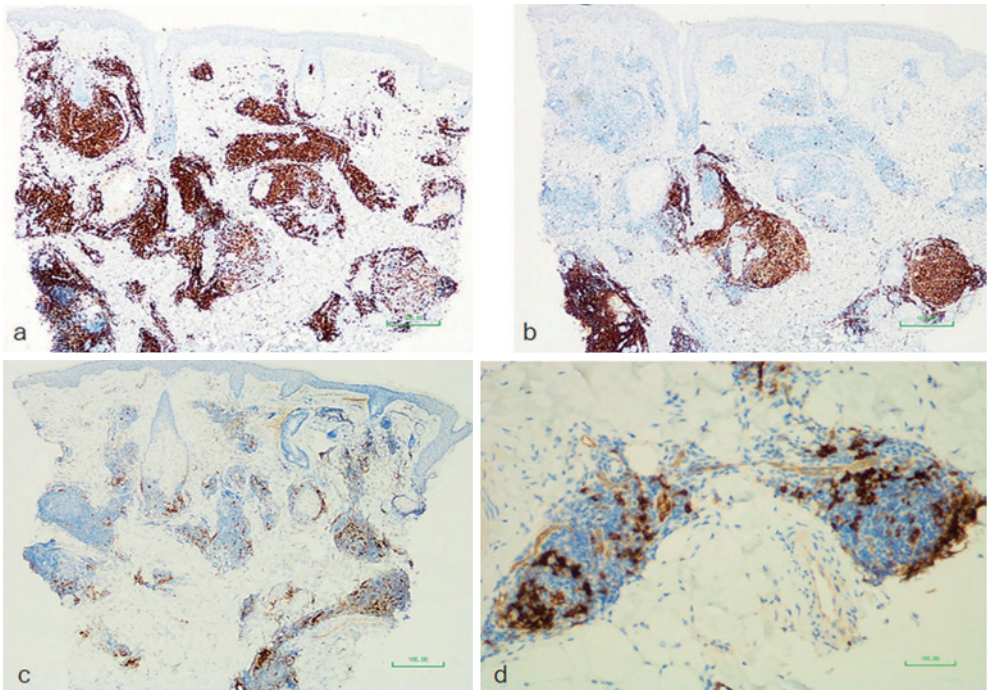

Fig. 3 Immunohistochemical staining showed that the infiltrates comprised CD3+ cell clusters (a) and CD20+ cell clusters (b) and included numerous CD123+ cells (c, d). Original magnification: (a, b, c) ×40, and (d) ×100.

LE that differentiate it from pseudolymphoma were the presence of interface dermatitis, clusters of pDCs, and dermal mucin deposition. The present case satisfied the latter two findings. Moreover, the clinical features—an erythematous plaque on the face—were consistent with those seen in LET. In LET, epidermal involvement is usually not noted[1], which differs from the presentation of other cutaneous forms of LE, like discoid LE or subacute cutaneous LE.

Although the pathogenesis of LET is not well understood, one hypothesis is that stress factors, including ultraviolet rays or smoking[2], induce apoptosis of epidermal keratinocytes and release of self-DNA, which might be internalized into endosomes of pDCs that stimulate Toll-like receptor 9 and induce secretion of interferon-α (IFN-α)[6]. Secreted IFN-α might act on dermal dendritic cells or macrophages and induce secretion of tumor necrosis factor-α (TNF-α) or interleukin-1β (IL-1β)[7,8]. These cytokines could further act on fibroblasts or endothelial cells to induce expression of hyaluronan synthase, thereby promoting synthesis of hyaluronan[9,10] and ultimately leading to dermal mucinosis. IFN-α secreted from pDCs might also act on endothelial cells, dendritic cells, or macrophages to induce secretion of chemokines CXCL9/10, promoting infiltration of type 1 T cells[11]. Moreover, secretion of chemokine CXCL13[12] by the IFN-α-activated cells above, might promote the infiltration of B cells. IFN-γ, possibly released from type 1 T cells, might also potentiate hyaluronan synthesis by fibroblasts or endothelial cells[8].

HCQ is reported to be effective for LET and might increase endosomal pH and suppress activation of Toll-like receptor 9 in pDCs[13]. This suppresses IFN-α secretion and thus IFN-α-induced secretion of TNF-α or IL-1β. Our patient exhibited remarkably dense infiltration of T and B cells, which might be insufficiently controlled by hydroxychloroquine alone and may necessitate additional treatment with prednisolone for complete resolution, owing to its immunosuppressive effects. In Western countries, other antimalarials, such as chloroquine 125-250 mg/day or mepacrine 50-100 mg/day, can be used in combination with HCQ or as monotherapy if the disease cannot be controlled with HCQ alone[2]. Because those antimalarials are not approved for use in Japan, we selected low-dose systemic corticosteroid. As second-line systemic treatments for LET, dapsone, mycophenolate mofetil, or methotrexate might be used in combination with HCQ; however, data on the effectiveness of these agents are lacking[2].

In conclusion, we described a case of LET with pseudolymphomatous infiltrates. Activation of pDCs might have caused dermal mucinosis and dense perivascular

and periadnexal infiltration of T cells and B cells. Dermal mucinosis and the presence of numerous pDCs aid in differentiating LET from pseudolymphoma.

Conflict of Interest: The authors declare no conflict of interest.

References

1. Kuhn A, Richter-Hintz D, Oslislo C, Ruzicka T, Megahed M, Lehmann P. Lupus erythematosus tumidus--a neglected subset of cutaneous Lupus erythematosus: report of 40 cases. Arch Dermatol. 2000 Aug 1;136(8):1033−41.
2. Patsinakidis N, Kautz O, Gibbs BF, Raap U. Lupus erythematosus tumidus: clinical perspectives. Clin Cosmet Investig Dermatol. 2019 Oct 1;12:707−19.
3. Furukawa F, Muto M. Ethnic differences in immunogenetic features and photosensitivity of cutaneous lupus erythematosus. Arch Dermatol Res. 2009 Jan;301(1):111−5.
4. Bergman R. Pseudolymphoma and cutaneous lymphoma: facts and controversies. Clin Dermatol. 2010 Sep-Oct;28 (5):568−74.
5. Pereira A, Ferrara G, Calamaro P, et al. The histopathological spectrum of pseudolymphomatous infiltrates in cutaneous lupus erythematosus. Am J Dermatopathol. 2018 Apr;40(4):247−53.
6. Obermoser G, Schwingshackl P, Weber F, et al. Recruitment of plasmacytoid dendritic cells in ultraviolet irradiation-induced lupus erythematosus tumidus. Br J Dermatol. 2009 Apr;40(4):197−200.
7. Popovic K, Ek M, Espinosa A, et al. Increased expression of the novel proinflammatory cytokine high mobility group box chromosomal protein 1 in skin lesions of patients with lupus erythematosus. Arthritis Rheum. 2005 Nov;52(11):3639−45.
8. Gambichler T, Genc Z, Skrygan M, et al. Cytokine and chemokine ligand expression in cutaneous lupus erythematosus. Eur J Dermatol. 2012 May-Jun;22(3):319−23.
9. Campo GM, Avenoso A, Campo S, Angela D, Ferlazzo AM, Calatroni A. TNF-alpha, IFN-gamma, and IL-1beta modulate hyaluronan synthase expression in human skin fibroblasts: synergistic effect by concomital treatment with FeSO4 plus ascorbate. Mol Cell Biochem. 2006 Nov;292(1-2):169−78.
10. Chang LM, Maheshwari P, Werth S, et al. Identification and molecular analysis of glycosaminoglycans in cutaneous lupus erythematosus and dermatomyositis. J Histochem Cytochem. 2011 Mar;59(3):336−45.
11. Wenzel J, Zahn S, Mikus S, Wiechert A, Bieber T, Tuting T. The expression pattern of interferon-inducible proteins reflects the characteristic histological distribution of infiltrating immune cells in different cutaneous lupus erythematosus subsets. Br J Dermatol. 2007 Oct;157(4):752−7.
12. Denton AE, Innocentin S, Carr EJ, et al. Type I interferon induces CXCL13 to support ectopic germinal center formation. J Exp Med. 2019 Mar 4;216(3):621−37.
13. Sacre K, Criswell LA, McCune JM. Hydroxychloroquine is associated with impaired interferon-alpha and tumor necrosis factor-alpha production by plasmacytoid dendritic cells in systemic lupus erythematosus. Arthritis Res Ther. 2012 Jun 27;14(3):R155.

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