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Systemic sclerosis complicated with localized scleroderma-like lesions induced by Köbner phenomenon

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ABSTRACT

Background: Scleroderma is a chronic disease of unknown etiology characterized by skin fibrosis and is divided into two clinical entities: systemic sclerosis (SSc) and localized scleroderma (LSc). In general, LSc is rarely complicated with SSc, but a certain portion of SSc patients manifests bilateral symmetric LSc-like lesions on the trunk and extremities.
Objective: We investigated SSc patients with LSc-like lesions to clarify the underlying pathophysiology.
Methods: Nine SSc cases complicated with LSc-like lesions were clinically and histologically characterized.
Results: SSc patients with LSc-like lesions exhibited multiple progressive hyper- and/or hypo-pigmented plaques with mild sclerosis symmetrically distributed on the trunk and extremities, especially abdominal region. In histological assessment, epidermal IL-1α expression was elevated in both forearms and LSc-like lesions of these patients to a greater extent than in forearms of control patients (SSc patients without LSc-like lesions). Of note, the infiltration and degranulation of mast cells were evident throughout the dermis of LSc-like lesions, while detectable to a lesser extent in forearms of SSc patients with LSc-like lesions and control patients.
Conclusion: The epidermis of SSc patients with LSc-like lesions seems to possess an inflammatory phenotype, leading to the activation of mast cells in the dermis of mechanically stressed skin. Köbner phenomenon may be involved in the induction of LSc-like lesions in a certain subset of SSc.

1. Introduction

Scleroderma is a chronic disease of unknown etiology characterized by skin fibrosis and is divided into two clinical entities: systemic sclerosis (SSc) and localized scleroderma (LSc, or morphea) [1]. SSc is a multisystem autoimmune and vascular disorder resulting in extensive tissue fibrosis of the skin and certain internal organs [2]. LSc differs from SSc in that it is not accompanied by Raynaud's phenomenon, acrosclerosis, and internal organ involvement, and is classified into 5 subtypes; circumscribed morphea, linear scleroderma, generalized morphea, pansclerotic morphea, and mixed morphea [3].

Although LSc is a different entity from SSc, coexistence of SSc with LSc or LSc-like skin lesions has been reported [4]. Apart from typical LSc, LSc-like lesions are generally characterized by multiple hyperpigmented plaques with mild skin sclerosis. Tissue fibrosis of typical LSc possibly spreads to subcutaneous tissues, including fat, fascia, tendon, and muscle, with variable degrees of severity, while tissue fibrosis is generally mild and restricted to the dermis in LSc-like lesions. Importantly, LSc-like plaques are mostly seen on the upper arms, lateral forearms, knees, waist, lumbar area, and back with a symmetric distribution. Although a potential contribution of Köbner phenomenon to the development of LSc-like lesions is proposed based on the characteristic distribution of plaques [5], it still remains unknown why such LSc-like lesions are complicated in a certain proportion of SSc patients.

We have recently proposed a new disease hypothesis of SSc that the deficiency of transcription factor Friend leukemia virus integration 1 (Fli1) in epithelial cells drives autoimmunity and selective organ fibrosis in the skin and esophagus through thymic defect and aberrantly activated squamous epithelia, respectively [6]. Importantly, epithelial cell-specific *Fli1* knockout mice lacking

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mature B cells and T cells (*Fli1*$^{flox/flox}$;*K14*-Cre, *Rag1*$^{-/-}$) develop dermal and esophageal fibrosis accompanied by the infiltration of mast cells (unpublished data), indicating that the activation of squamous epithelia induces tissue fibrosis through the activation of innate immunity including mast cells. This phenomenon seems to be partly mediated by IL-1α overproduction in squamous epithelia. This theory may be applicable to human SSc because IL-1α is up-regulated in SSc keratinocytes and stimulates type I collagen production in cultured dermal fibroblasts [7]. Also, IL-1α promotes the secretion of IL-6, a key driver of SSc development, from mast cells [8]. Given that IL-1α is basically pooled in squamous epithelia and secreted from those cells in response to various stimuli [9,10], this cytokine may be involved in the development of Köbner phenomenon-related sclerotic plaques in SSc.

Based on these backgrounds, to better understand the developmental mechanism underlying LSc-like lesions, we examined the histological features of such lesions in 9 patients with SSc.

2. Materials and methods

2.1. Ethical statement

This study was performed according to the Declaration of Helsinki and approved by ethical committees (University of Tokyo Graduate School of Medicine). Written informed consent was obtained from all the participants.

2.2. Patients

Nine female patients with SSc and LSc-like lesions, who visited us between 2001 and 2013, were retrospectively included. All patients had anticentromere antibody (ACA) detected by enzyme-linked immunosorbent assay (ELISA) and fulfilled the new classification criteria of SSc [11].

2.3. Histological analysis

In each SSc patient, skin biopsy samples were obtained from the forearm and LSc-like lesions on the trunk. Epidermal atrophy, spongiosis, vacuolar changes or liquefaction degeneration, satellite cell necrosis, basal pigmentation, melanin incontinence, perivascular infiltrate, periappendageal infiltrate, and dermal fibrosis were semi-quantitatively evaluated in hematoxylin & eosin staining and classified into four grades: –, absent; +, mild; ++, moderate and +++, severe. We also performed IL-1α immunostaining using Vectastain ABC kit (Vector Laboratories, Burlingame, CA) and anti-IL-1α antibody (sc-271618, Santa Cruz Biotechnologies, Santa Cruz, CA), and toluidine blue staining on formalin-fixed, paraffin-embedded skin sections.

2.4. Statistical analysis

Frequency was analyzed by Fisher's exact probability test. Mann-Whitney *U* test with Bonferroni correction was used for multiple comparison. If values are all the same in any single group, Kruskal-Wallis test followed by Dunn's multiple comparison test was used because Mann-Whitney *U* test is not applicable.

3. Results

3.1. Clinical features of typical cases

Patient 1 was a 45-year-old woman who visited us because of Raynaud's phenomenon and skin pigmentation. She first noticed Raynaud's phenomenon, and pigmentation on the neck and upper limbs 5 years before, the lower legs 2 years before, and the abdomen a year before. On the first examination, she presented with sclerodactyly, nailfold bleeding, cyanosis on the digits and toes, and pitting scars on the fingertips. Irregularly shaped sclerotic plaques with pigmentation were seen on the neck, chest, upper arms, lower abdomen, waist, thighs, and knees symmetrically (Fig. 1A and 1B). Laboratory data showed that anti-nuclear antibody was positive (discrete speckled, ×320), and ACA and anti-mitochondrial M2 antibody were also positive by ELISA. Skin biopsy specimens taken from the forearm and abdomen exhibited thickened collagen bundles in the entire dermis. Inflammatory cell infiltrates mainly composed of lymphocytes were slightly observed around the dermal blood vessels and sweat glands; more densely in the specimen taken from the abdomen than in that from the forearm (Fig. 1C–F). Moreover, slight vacuolar changes and melanin incontinence were seen in the abdominal lesion (Fig. 1D and 1F). Interstitial lung disease (ILD) and pulmonary hypertension (PH) were not detected. We diagnosed this patient as being suffering from SSc with LSc-like lesions. She was treated by topical corticosteroid for sclerotic lesions.

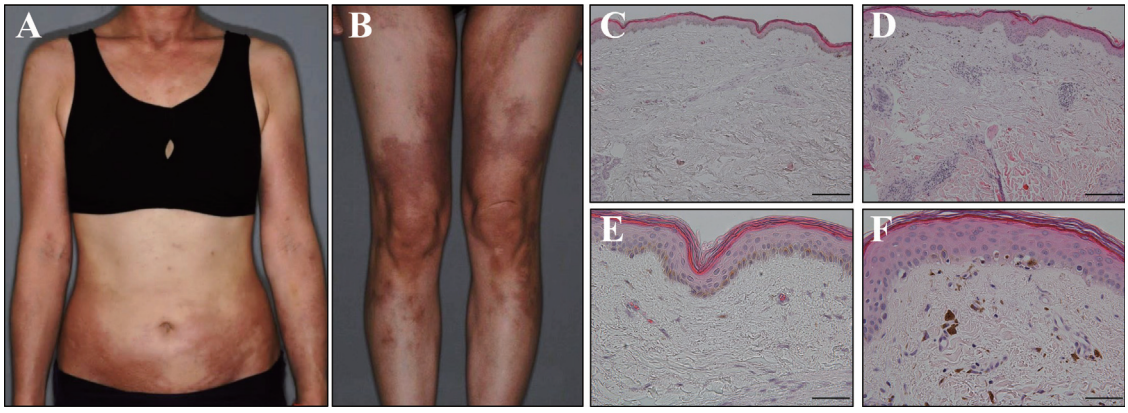

Fig. 1. Clinical and histological features of Patient 1.
(A, B) Irregular sclerotic plaque lesions with pigmentation were seen on her neck, chest, upper arms, lower abdomen, waist, thighs, and knees symmetrically. (C–F) Inflammatory cell infiltrates mainly composed of lymphocytes were observed around dermal blood vessels and sweat glands in both the forearm and abdominal lesions. In comparison between the forearm and abdominal lesions, inflammatory cells were more densely infiltrated in the specimen from the abdominal lesion (D: ×100, F: ×400) than in that from the forearm (C: ×100, E: ×400). Scale bars; 200 μm (C, D) and 50 μm (E, F).

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