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# Psoriatic Arthritis Complicating Systemic Sclerosis: Possible Involvement of M2 Macrophages

Toshifumi Yamaoka, Tomoko Inoue, Shun Kitaba, Akinori Yokomi, Hiroaki Azukizawa, Mika Terao, Hiroyuki Murota, Mari Higashiyama[1], Ichiro Katayama

*Department of Dermatology, Osaka University Graduate School of Medicine, [1]Department of Dermatology, Nissay Hospital, Osaka, Japan*

Dear Editor:

Psoriatic arthritis (PsA) is a seronegative inflammatory arthritis that occurs in the presence of psoriasis. The synovial macrophages are a major source of proinflammatory cytokines[1]. The subset of macrophages that expresses alternatively activated macrophages (M2 macrophages) is usually greater in number in PsA synovitis than in rheumatoid arthritis synovitis[2]. Systemic sclerosis (SSc) is a rheumatological disorder characterized by excessive fibrosis and microvascular damage of the skin and various internal organs. The presence of macrophage infiltrates and increased numbers of M2 macrophages in fibrotic areas have been reported[3].

A 44-year-old Japanese man developed scaly erythema that had been present on the trunk and lower and upper extremities for 40 years. A primary care doctor had diagnosed his condition as psoriasis. His previous treatments included topical corticosteroid therapy, topical psoralen ultraviolet-A therapy, or oral cyclosporin. Sacroiliitis was also associated with the skin symptoms. For the previous 4 years, the scaly erythema had gradually improved but was then complicated by sclerodactylia. On examination, a high anti-nuclear antibody (ANA) titer with homogeneous, speckled, and nucleolar patterns (×640) was present. Detailed analysis of the ANA revealed that there was a significant increase in anti-topoisomerase I antibody (152 U/ml). Rheumatoid factor was negative. From these results, the presumptive diagnosis was SSc complicated by PsA, and the patient was admitted to our hospital. Psoriatic plaque was present on the elbows of the patient (Fig. 1A). The modified Rodnan total skin thickness score value of 22 was used to grade the degree of skin sclerosis (Fig. 1B). The levels of T helper 2 cytokines, such as interleukin (IL)-4 (17.0 pg/ml) and transforming growth factor (TGF)-$\beta$1 (15.1 ng/ml), were elevated. The serum Krebs von den Lungen-6 (1,182 U/ml) and surfactant protein D (226 ng/ml) levels were elevated, and high-resolution computed tomography revealed the presence of a bilateral consolidation of both lower lobes with peripheral ground glass opacity. Skin biopsies from the elbow and the forearm revealed the presence of markedly elongated rete ridges with parakeratosis (Fig. 1C), and sclerotic change that ascended from the lower dermis (Fig. 1D). We also performed immunostaining for CD68 (Fig. 1E, F) and CD163 (Fig. 1G, H) in lesional skin biopsy samples. Subequal infiltrated dermal cells expressed CD68, which suggested that macrophages infiltrated both types of samples of lesional skin. Furthermore, the numbers of CD163-positive cells were increased in lesional skin from SSc. This result suggests that M2 macrophages were increased in lesional skin from SSc compared with lesional skin from PsA (Fig. 1E~H).

Polarized macrophages have been broadly classified into two groups: M1 and M2 macrophages. Tissue macrophages can exist in different activation states. They can be proinflammatory macrophages (M1; activated by interferon-$\gamma$ or lipopolysaccharide) or anti-inflammatory macrophages (M2; activated by TGF-$\beta$ or IL-4)[4]. They participate in tissue remodeling, immune modulation, parasite clearance, and tumor progression[5]. In this patient, M2 macrophages may be one of the key regulating cell types involved in the

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**Corresponding author:** Toshifumi Yamaoka, Department of Dermatology, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita Osaka 565-0871, Japan. Tel: 81-6-6879-3031, Fax: 81-6-6879-3039, E-mail: yamaoka@derma.med.osaka-u.ac.jp

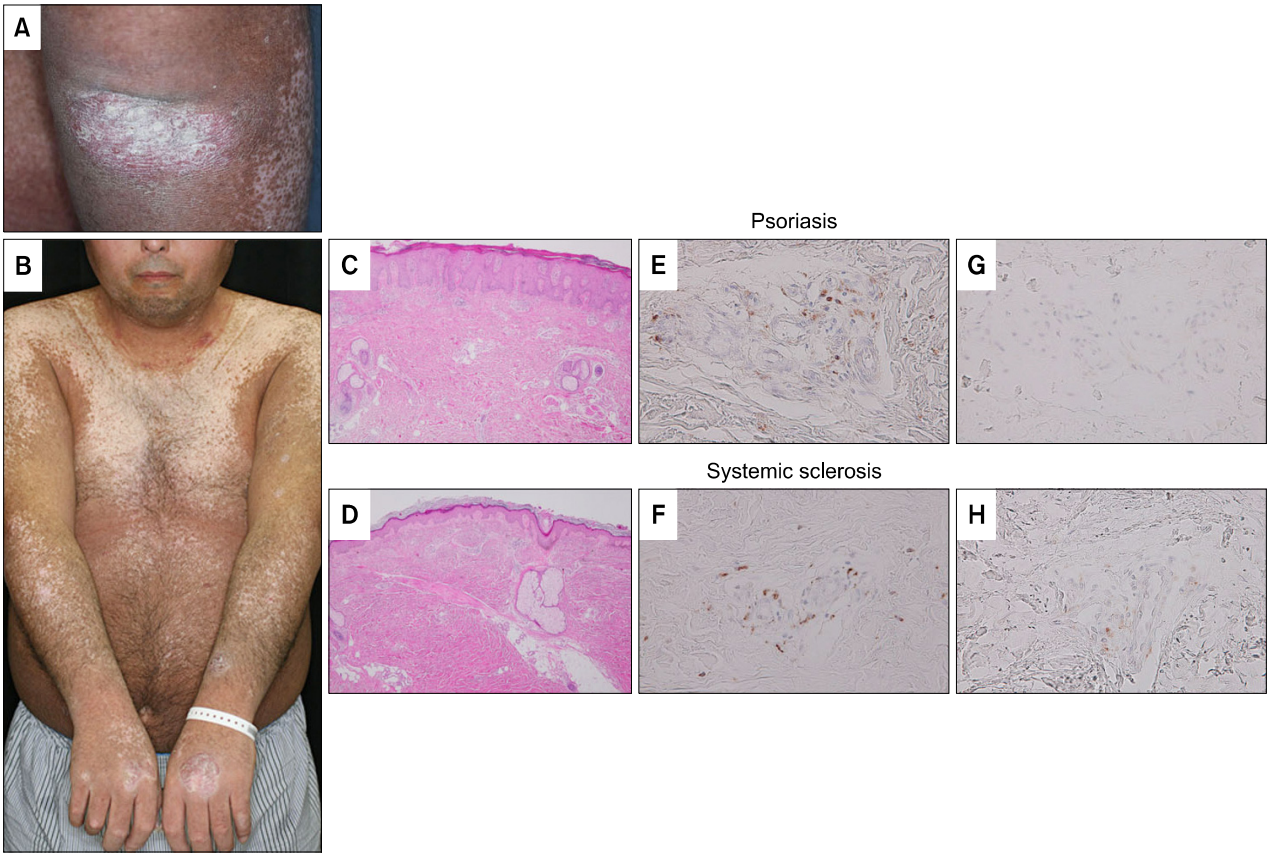


**Fig. 1.** Clinical and histopathological manifestations in the patient. (A) Psoriatic skin lesion affecting the elbow. (B) Widespread skin thickening, progressing from the fingers to the trunk. (C) The skin biopsy specimen from the elbow has characteristics consistent with psoriasis (including parakeratosis), regular acanthosis, thinning of the suprapapillary plate, hypogranulosis, and mild superficial perivascular and interstitial infiltrates. (D) Biopsy specimen from the sclerotic lesional skin of the forearm. Thickened and homogeneous collagen bundles were visible (C, D: H&E, ×40). (E, F) Immunohistochemical staining for CD68 (macrophages). Each lesional skin sample had nearly equal positive CD68 levels in this dermis. (G, H) Immunohistochemical staining for CD163 (M2 macrophages). CD163-positive cells were increased in the lesional scleroderma (E∼H: ×400).

clinical manifestations. However, further investigations are needed for elucidating the involvement of M2 macrophages in skin disorders.

## REFERENCES

1. Vandooren B, Noordenbos T, Ambarus C, Krausz S, Cantaert T, Yeremenko N, et al. Absence of a classically activated macrophage cytokine signature in peripheral spondylarthritis, including psoriatic arthritis. Arthritis Rheum 2009;60:966-975.
2. Fuentes-Duculan J, Suárez-Fariñas M, Zaba LC, Nograles KE, Pierson KC, Mitsui H, et al. A subpopulation of CD163-positive macrophages is classically activated in psoriasis. J Invest Dermatol 2010;130:2412-2422.
3. Higashi-Kuwata N, Jinnin M, Makino T, Fukushima S, Inoue Y, Muchemwa FC, et al. Characterization of monocyte/macrophage subsets in the skin and peripheral blood derived from patients with systemic sclerosis. Arthritis Res Ther 2010;12:R128.
4. Aron-Wisnewsky J, Tordjman J, Poitou C, Darakhshan F, Hugol D, Basdevant A, et al. Human adipose tissue macrophages: m1 and m2 cell surface markers in subcutaneous and omental depots and after weight loss. J Clin Endocrinol Metab 2009;94:4619-4623.
5. Hao NB, Lü MH, Fan YH, Cao YL, Zhang ZR, Yang SM. Macrophages in tumor microenvironments and the progression of tumors. Clin Dev Immunol 2012;2012:948098.