

Immunohistochemical Similarities between Lichen Sclerosus et Atrophicus and Morphea: A Case Study

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Key Words

Lichen sclerosus et atrophicus · Morphea · Periostin · MMP-7 · MMP-28

Abstract

Both morphea and lichen sclerosus et atrophicus (LSA) are connective tissue diseases that mainly affect the skin. A recent report suggested that a substantial portion of morphea coexists with LSA. In this report, we describe a case of LSA on the abdomen accompanied by morphea; we employed immunohistochemical staining for periostin as well as MMP-7 and MMP-28, both of which are reported to facilitate fibrosis in the development of various organs, including skin. To our knowledge, this is first English language paper that demonstrates the immunohistochemical staining of periostin, MMP-7 and MMP-28 for morphea and LSA. Our present case might suggest possible mechanisms for the coexistence of two different sclerotic skin disorders.

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Introduction

Morphea is a connective tissue disease that mainly affects the skin [1]. A recent report suggested that 5.7% of morphea (27/472 cases) coexist with lichen sclerosus et atrophicus (LSA) [1]. LSA is a connective tissue disease that predominantly affects the anogenital area and oral cavity. Although an autoimmune hypothesis has been proposed for LSA and morphea [2], the pathogenesis of LSA is still under discussion. In this report, we describe a case

of LSA on the abdomen accompanied by morphea; we employed immunohistochemical (IHC) staining for periostin as well as MMP-7 and MMP-28, both of which have been reported to facilitate the development of fibrosis in various organs [3–9]. Notably, MMP-28 polarized skin resident macrophages into alternative activated M2 macrophages, which were previously reported to promote wound healing and fibrosis of skin [10–13]. To our knowledge, this is first English language paper that demonstrates the IHC staining of periostin, MMP-7 and MMP-28 for morphea and LSA, and our present case might suggest possible mechanisms for the coexistence of two different sclerotic skin disorders.

Case Report

A 74-year-old woman consulted us for a 6-year history of scleroderma on her extremities. She had been treated in a private clinic for a morphea with narrow-band UVB without any improvement. On her initial visit, physical examination revealed asymptomatic, waxy, whitish papules on the left side of the abdomen (fig. 1a, b). In addition, multiple sclerosing plaques were scattered on the extremities (fig. 1c). A biopsy specimen from the left abdomen revealed hyperkeratosis with follicular plugging, atrophy of the stratum malpighii with hydropic degeneration of basal cells, and pronounced edema and homogenization of the collagen (fig. 1d). In contrast, a specimen from the right knee revealed interstitial lymphoplasmacytic infiltrates among the slightly thickened collagen bundles in the reticular dermis (fig. 1e). A full blood count and biochemical profile were within the normal range. Serum levels of ANA and other autoantibodies were below normal range. From the above findings, we diagnosed this patient as LSA on the abdomen accompanied by morphea. We treated her with oral prednisolone 40 mg/day for 2 weeks and tapering 5 mg every 2 week, and her initial eruption gradually improved.

To further investigate the possible mechanisms responsible for the coexistence of these sclerosing disorders, we employed IHC staining. IHC staining for periostin revealed dense deposits of periostin in areas with dermal fibroblasts (fig. 2a, b). Moreover, MMP-7 (fig. 2c, d) and MMP-28 (fig. 2e, f) staining revealed that both MMP-7 and MMP-28 were highly expressed at the basal layer by spindle cells in the dermis in the lesional skin of LSA and morphea. As we previously reported [3], there was no staining of MMP-7 and MMP-28 at the edge of the LSA and morphea (data not shown). We compared the expression of periostin, MMP-7 and MMP-28 in our case with 3 cases of sporadic morphea and 3 cases of sporadic LSA (table 1). For the analysis of IHC stainings, we semiquantitatively analyzed the intensity of IHC staining by scoring on a semiquantitative scale as previously reported [14]. In addition, IHC staining for CD163 (fig. 2g, h) and CD206 (fig. 2i, j) revealed prominent CD163+CD206+ macrophages infiltrating around the perivascular and interstitial areas of the lesions from LSA and morphea.

Discussion

Previous reports suggested that morphea occasionally coexists with LSA [1]. Both LSA and morphea are connective tissue diseases and an autoimmune hypothesis has been proposed for LSA and morphea. For example, Cooper et al. [2] suggested a high association between LSA and other autoimmune diseases, which can be explained by the presence of highly specific antibodies targeting extracellular matrix protein-1. Notably, LSA has also been reported to establish squamous cell carcinoma, though the mechanism is still unknown [15].

Periostin is a matrix cellular protein involved in modulating cell function, including the production of chemokines related to monocytes/macrophages (CCL2, CCL4, CCL7) and pro-inflammatory cytokines such as IL-1 β and TNF- α from fibroblasts, and has a role in fibrosing diseases such as bleomycin-induced pulmonary fibrosis [4]. In addition, previous reports suggested that periostin contributes to tumor progression [16]. Concerning skin diseases, the expression of periostin, which is regulated by TGF- β , was significantly increased in keloid and hypertrophic scar tissue compared with normal skin [5]. In our present case, IHC staining for periostin revealed dense deposition of periostin in areas with dermal fibroblast in the lesional skin of LSA and morphea. Notably, in such areas of the skin, CD163+ macrophages and CD206+ cells were prominent in both LSA and morphea, which might suggest the production of macrophage-related chemokines from fibroblasts that facilitate the recruitment of macrophages, and these M2-like macrophages might contribute to the fibrosis in the lesional skin.

Alternatively activated M2 macrophages express the scavenger receptor (CD163), the mannose receptor (CD206) and IL-10, which lead M2 macrophages to participate in parasite clearance, tissue remodeling, immune modulation and tumor progression [10]. Several factors have been reported to contribute to the polarization of M1/M2 macrophages [10]. Among them, MMP-28 (epilysin) has been reported as one of the important regulators of macrophage polarization [11, 12]. MMP-28 is a member of the MMP family that is highly expressed in the testis. In the dermatological fields, MMP-28 is reported to play a role in the remodeling of the newly formed basement membrane during wound repair [13]. In our present case, as we expected, substantial numbers of CD163+ macrophages and CD206+ cells were detected in the same areas as MMP-28-expressing cells in the lesional skin of LSA and morphea, which might suggest a correlation between MMP-28 and M2 macrophages in our case. In addition to MMP-28, MMP-7-expressing cells and the deposition of MMP-7 were detected in the dermal, macrophage-infiltrating area. Notably, MMP-7 has also been reported to contribute to both sclerosing and tumor progression [6, 17]. Although the immunomodulatory effects of MMP-7 on M2 macrophages are still unknown, MMP-7 might have an indirect effect on the macrophages, facilitating the recruitment of other immune cells [18].

In this report, we describe a case of LSA accompanied by morphea; we employed IHC staining for periostin as well as MMP-7 and MMP-28, both of which have been reported to facilitate the development of fibrosis the various organs, including skin [3–9]. In addition, recent reports also suggested that MMP-28 is an important regulator of macrophage polarization, promoting M2 function [11, 12]. As we expected, our present case showed substantial numbers of CD163+ macrophages and CD206+ cells in the lesional skin of LSA and morphea. Our present case might suggest possible mechanisms for the coexistence of two different sclerotic skin disorders. Since the number of analyzed cases is small and IHC analysis only examines a single time point within the life of a tumor, further cases are needed to gain additional insight into the pathomechanisms of LSA and morphea.

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Table 1. Summary of three cases of sporadic LSA, three cases of morphea and the present case

	Periostin	MMP-7	MMP-28
<i>LSA</i>			
Case 1	+++	++	+++
Case 2	+++	+++	+++
Case 3	++	++	+++
Present case	+++	+++	+++
<i>Morphea</i>			
Case 1	+++	+++	+++
Case 2	++	++	++
Case 3	+++	+++	+++
Present case	+++	+++	+++

The intensity of IHC staining was scored on a semi-quantitative scale (+ = weak; ++ = moderate; +++ = intense).

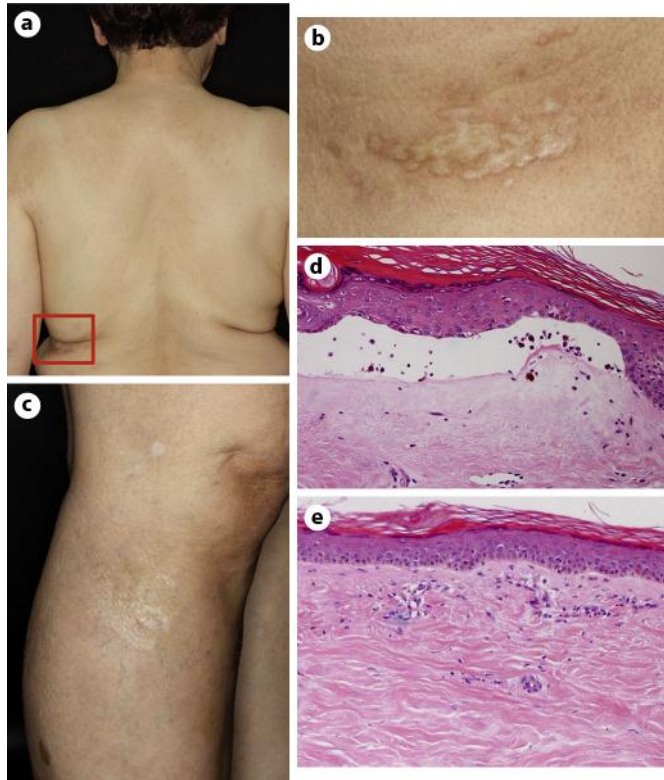


Fig. 1. **a, b** Waxy, whitish papules on the left side of the abdomen. **c** Multiple sclerosing plaques were scattered on the extremities. **d** A biopsy specimen from the left abdomen revealed hyperkeratosis with follicular plugging, atrophy of the stratum malpighii with hydropic degeneration of basal cells, and pronounced edema and homogenization of the collagen. Original magnification: $\times 200$. **e** A specimen from the right knee revealed interstitial lymphoplasmacytic infiltrates among the slightly thickened collagen bundles in the reticular dermis. Original magnification: $\times 200$.

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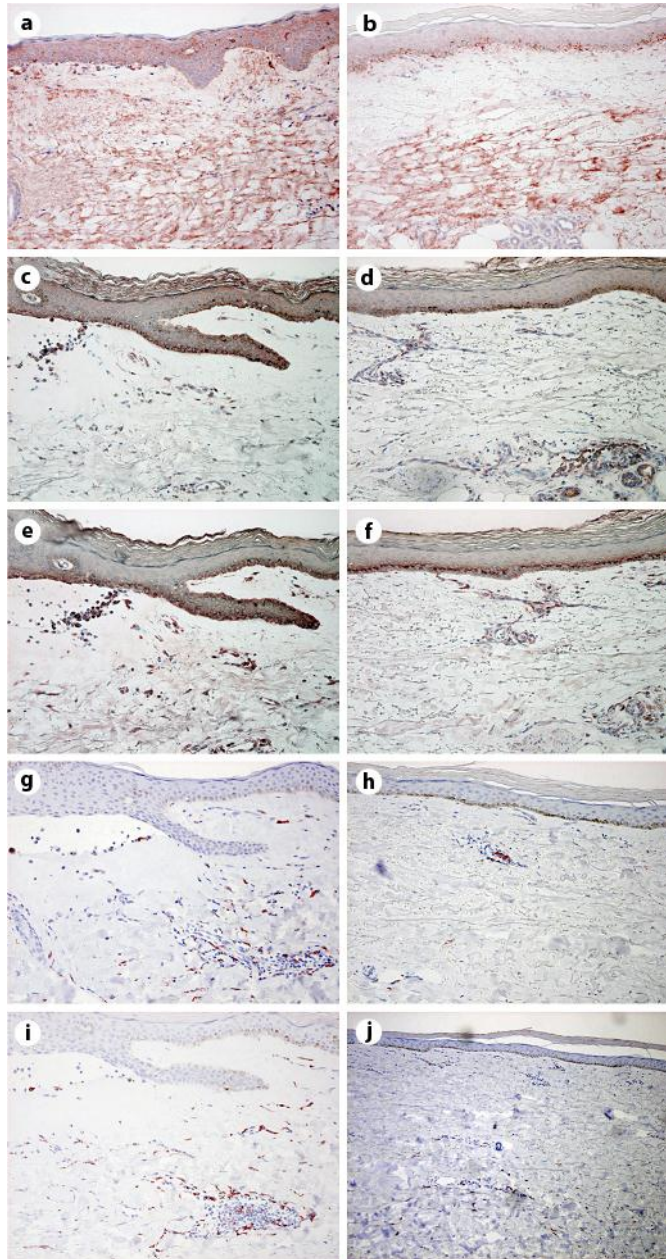


Fig. 2. Paraffin-embedded tissue samples from the abdomen (a, c, e, g, i) and the right knee (b, d, f, h, j) were deparaffinized and stained with anti-periostin antibody (a, b), anti-MMP-7 antibody (c, d), anti-MMP-28 antibody (e, f), anti-CD163 antibody (g, h) or anti-CD206 antibody (i, j). The sections were developed with liquid permanent red. Original magnification: $\times 100$ (a, b, h, j), $\times 200$ (c, d, e, f, g, i).