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Morphea in a Crohn's disease patient undergoing ustekinumab treatment

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The pathophysiology of morphea is incompletely understood, but it comes down to an imbalance between collagen synthesis and breakdown[1]. Various etiologic factors are thought to induce endothelial injury, inducing the release of cytokines that increase the expression of vascular cell adhesion molecules[1]. Medications are rarely associated with the occurrence of morphea, but a recent literature review identified 15 reported cases of drug-induced morphea[2]. Ustekinumab, which is a monoclonal antibody to the p40 subunit of interleukin-12 and interleukin-23, is widely used as a therapy for psoriasis and inflammatory bowel disease (IBD). The present report outlines a unique case of morphea that developed during ustekinumab treatment for Crohn's disease.

A 17-year-old Japanese male complained of abdominal pain and diarrhea. A colonoscopy showed inflammatory polyposis in the ascending colon. He was diagnosed with Crohn's disease, which was treated with the anti-TNFα antibody adalimumab. At age 18, he developed dizziness, vomiting and coughing, and the biologic was switched from adalimumab to ustekinumab. After 1 year on ustekinumab under the treatment protocol recommended by the supplier, a hyperpigmented sclerotic plaque appeared on the left axilla (Fig. 1A, B) with no apparent history of trauma, and acne vulgaris appeared on the face, chest and back. The acne might have been associated with the ustekinumab treatment. The acne vulgaris was exacerbated once, immediately after the ustekinumab administration, but it was controlled well afterward. A skin biopsy from the left axilla showed significant thickening of the dermis, with thick, densely packed bundles of collagen fibers (Fig. 1C, D). CD34 expression was largely absent in the lesional skin of the patient but was present in the control skin (Fig. 1E, F). Serum anti-nuclear, anti-centromere, anti-Scl-70, and anti-RNA polymerase 3 antibodies were all negative. His axillar eruption was diagnosed as morphea and was treated with topical

steroid ointments, which only minimally improved the lesion. At three years of ustekinumab treatment with careful follow-up for acne vulgaris and morphea, he had no recurrence of Crohn's disease. However, the area of morphea expanded gradually.

Lee et al. reported that CD34 stromal expression is inversely proportional to smooth muscle actin expression and reflects the extent of morphea, suggesting that the severity of the loss of CD34-positive dermal dendritic cells can be a useful marker for morphea extent and severity[3]. Our results (Fig. 1E, F) are consistent with the immunohistochemical findings of their report.

Extracutaneous comorbidities in morphea patients are considered to be extremely rare, although the literature describes various extracutaneous comorbidities in patients with morphea[4]. Therefore, the coexistence of morphea and IBD seems to be a very rare finding. Steuer et al. reported morphea in an ulcerative colitis patient undergoing treatment with ustekinumab[1]. In addition, morphea in a psoriasis patient undergoing ustekinumab treatment was reported[5]. To our knowledge, the present patient is the first reported Crohn's disease case to develop morphea during ustekinumab treatment.

Our patient showed morphea after switching from adalimumab to ustekinumab. To our knowledge, only two cases of morphea that developed during adalimumab treatment have been reported[6, 7]. Interestingly, enhanced TNF-α expression was reported to be associated with disease severity and activity in localized scleroderma[8]. Furthermore, in systemic sclerosis, ustekinumab treatment for psoriasis was reported to improve skin tightening. From these data, it can be speculated that TNF-α blockade may be a potential treatment for morphea. However, in some cases including the present patient, morphea developed during treatment with biologics against TNF-α signaling[1, 5-7]. TNF-α might have conflicting actions as a stimulator and an inhibitor

in the pathogenesis of morphea[9].

In localized scleroderma, the imbalance between Th1/Th2/Th17 cell subsets drives inflammation in the early stages of the disease (Th1 and Th17 predominant) and promotes fibrosis in the later stages (Th2 predominant). Ustekinumab suppresses the differentiation of CD4-positive naive T cells into Th1 and Th17 cells. As a result, the physiological activity of Th1 and Th17 is suppressed, resulting in dysregulation of the Th1/Th2/Th17 balance. Therefore, ustekinumab might have been a trigger that induced the morphea in our case, although we cannot exclude the possibility that the occurrence of morphea and ustekinumab treatment in the present patient with Crohn's disease were merely coincidental. The further accumulation of similar cases is needed to confirm the molecular pathogenesis of morphea during ustekinumab treatment.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Figure legends

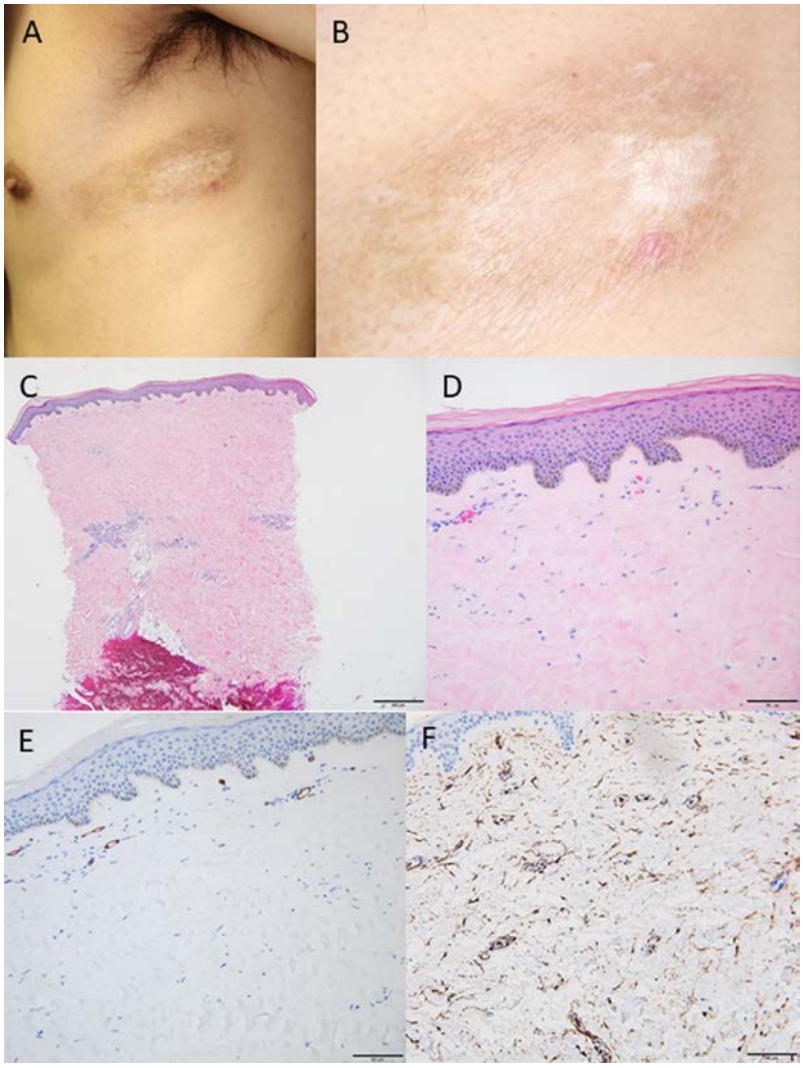

Figure 1. Clinicopathological features of the present patient.

(A) A hyperpigmented sclerotic plaque on the left axilla. (B) The morphea plaque has a shiny appearance at the center and hyperpigmentation with a scaly surface at the periphery. (C, D) Histopathological features of a skin biopsy specimen from the morphea lesion. Thickening of the dermis (C). Extensive deposition of collagen fibers parallel to the skin surface and decreases in the number of cutaneous adnexal units and blood vessels in the dermis (D). (E, F) Immunohistochemistry for CD34 in the morphea lesion; CD34 stromal staining is mostly negative in the lesional skin sample from the present patient (E), versus the positive staining in a control skin sample (F). Scale bars, 500 μm (C), 100 μm (D-F).