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LETTER TO THE EDITOR

Multiple Autoimmune Skin Manifestations in a Patient with Crohn's Disease Treated with a Tumor Necrosis Factor-Alpha Blocker

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Dear Editor:

Tumor necrosis factor (TNF)-alpha is an important mediator of chronic inflammation. TNF-alpha inhibitors have been shown to be effective in the treatment of several chronic inflammatory diseases. However, various immune-mediated disorders are reportedly induced by anti-TNF-alpha therapies, including autoimmune skin conditions such as psoriasis, granuloma annulare, vasculitis, alopecia areata (AA), lupus erythematosus, skin sarcoidosis, lichenoid eruption, and vitiligo. Here, we report a case of concomitant multiple autoimmune dermatoses in a patient with Crohn's disease (CD) treated with infliximab.

A 51-year-old man presented to our unit for a few non-scarring patchy hair loss areas on the scalp. Circular areas of alopecia with otherwise normal skin were evident (Fig. 1A). Black dots and a few exclamation mark-like hairs were appreciable in addition to leucotrichia. He was diagnosed with AA. The patient had been affected by CD for approximately 20 years and had been treated with infliximab for the previous 3 months. A mild form of rheumatoid arthritis involving the proximal interphalangeal and metacarpophalangeal joints was also present. The patient had been previously treated, with unsatisfactory response, with several immunomodulatory agents, notably cyclosporin, azathioprin, adalimumab, and etanercept. The patient continued anti-TNF-alpha therapy with infliximab despite the diagnosis of AA. Topical steroids were recommended for the hair loss. One year later, the patient presented again to our unit for a cutaneous rash that had been present for approximately 2 months. Skin examination revealed numerous circular, raised, 2～3-cm weals surrounded by inflammatory rings and involving the entire body surface. A clinical diagnosis of chronic urticaria was made (Fig. 1B). Skin examination also revealed the presence of whitish circular maculae replacing the previous nevi, which were consistent with the clinical diagnosis of multiple halo nevi (Fig. 2A). Moreover, the previously observed AA had evolved into the universalis form (Fig. 2B). Despite the skin autoimmune manifestations, infliximab therapy was maintained because of the aggressiveness of the CD.

AA has been reported to appear during anti-TNF-alpha treatment[1]. It is believed that multiple cytokines, such as TNF-alpha, interleukin-1, and interferons, might be relevant to the autoimmune pathogenesis of AA because peribulbar inflammation is believed to inhibit hair growth. AA usually appears within the first 3 months of treatment, either *de novo* or as a relapse of a previous, usually inactive AA, and may be partial or universalis. Discontinuation of the treatment may result in rapid hair regrowth. Direct involvement of the anti-TNF-alpha molecule seems very likely owing to chronological data and the long-evoked autoimmune hypothesis regarding AA pathogenesis, although no specific immunological disturbance has ever been revealed in this peculiar setting. Chronic refractory urticaria has been treated with anti-TNF-alpha drugs[2]. Cases of urticaria induced by anti-TNF-alpha treatment have also been reported. These reactions suggest that potential immunogenic sites may appear either when a human monoclonal

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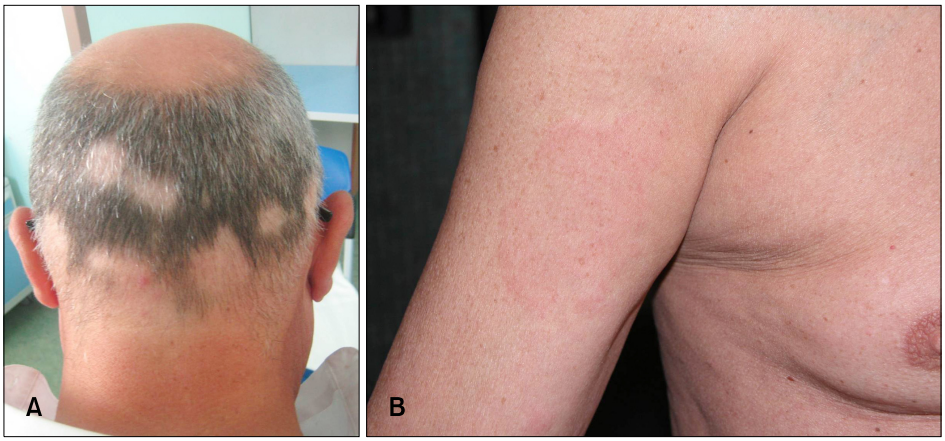

Fig. 1. (A) Circular areas of alopecia areata, (B) a circular, raised, 2～3-cm weal, surrounded by an inflammatory ring.

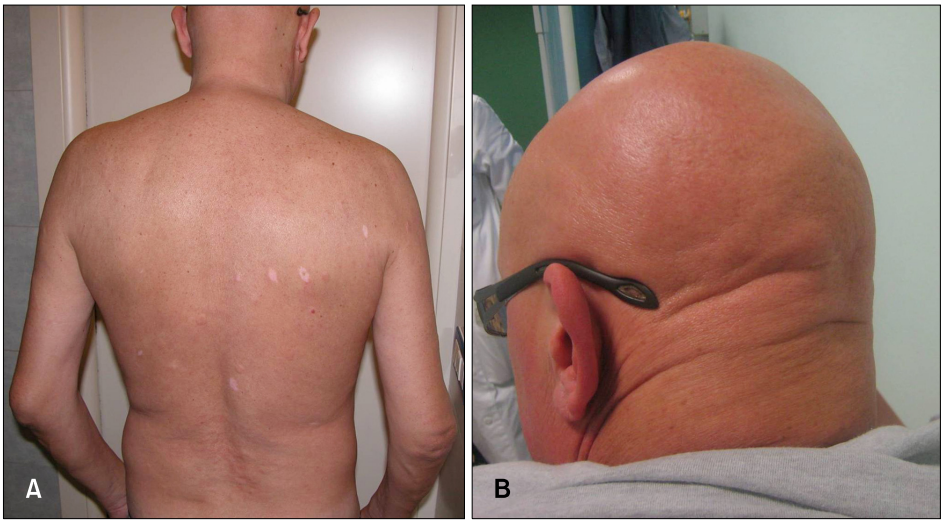

Fig. 2. (A) Multiple halo nevi on the back, (B) alopecia areata universalis.

(adalimumab) or a chimeric human-mouse TNF-alpha antibody (infliximab) complexes with TNF-alpha. Halo nevi have been reported to appear during infliximab therapy together with the worsening of AA[1]. In the literature, no other cases of halo nevi onset during anti-TNF-alpha treatment have been described. However, several cases of vitiligo onset in patients receiving infliximab[3] have been reported. In contrast, several cases of vitiligo improvement have been described in patients receiving infliximab[4].

The present patient with CD is an example of how infliximab use can cause the onset of concomitant autoimmune pathologies with different clinical presentations. Even if biotechnological drugs are considered to be the most innovative cure for several inflammatory diseases, these rare side effects should also be considered. These unwanted effects of TNF-alpha blockers are not predictable because the immune pathways involved in the autoimmune conditions that we described in the preceding paragraphs are not yet understood.

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