New-onset vitiligo as an unusual cutaneous reaction under ustekinumab therapy in patients with psoriatic arthritis

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Dear Editor,

Vitiligo, a common depigmenting autoimmune disorder of unknown etiology, is typically characterized by progressive loss of epidermal melanocytes. Although, various paradoxical cutaneous lesions (i.e. psoriasis, hidradenitis suppurativa, pyoderma gangrenosum) associated with the initiation of biological agents for inflammatory diseases have been reported, the development of vitiligo is an unusual event for patients receiving these treatments[1]. Herein, to the best of our knowledge, we present the first case of new-onset vitiligo in a patient receiving ustekinumab for the treatment of psoriatic arthritis (PsA).

A 33-year-old man with a 4-year history of PsA was admitted to our rheumatology clinic. Previous treatments with nonsteroidal anti-inflammatory drugs, methotrexate and leflunomide failed to control the disease activity. Etanercept treatment was started one year ago. After eight months of etanercept therapy the musculoskeletal findings were improved, but paradoxical psoriasis occurred. First, topical corticosteroid therapy was applied, then it was decided to continue with ustekinumab 45 mg subcutaneous injection at weeks 0 and 4 followed by every 12 weeks in combination with leflunomide. At the 16th week of ustekinumab therapy (3rd dose), the patient returned to our clinic due to hypopigmented lesions on the dorsum of the fingers which presented white coloration under Wood's light and clinically typical vitiligo (Figure 1). Predisposing factors associated with the development of vitiligo have been investigated. He had no personal or family history of depigmenting or autoimmune disease (i.e. thyroiditis, type 1 diabetes, pernicious anemia) associated with vitiligo. He did not have any clinical signs and symptoms attributable to connective tissue disorders or other autoimmune diseases. He also was not exposed to any chemicals that trigger vitiligo. In the autoimmune screening, the anti-nuclear antibody (ANA) was weakly positive (1:100) with a speckled pattern and the results of anti-double stranded DNA, rheumatoid factor, complement levels, anti-thyroid peroxidase and extractable nuclear antigen (ENA) profile were all negative. In this case, after possible etiologic factors associated with the development of vitiligo were ruled out, there was concern that vitiligo was induced by ustekinumab treatment.

Ustekinumab is a monoclonal antibody against the shared p40 subunit of interleukin-12/23. It is approved for the treatment of moderate-to-severe plaque psoriasis, PsA and inflammatory bowel disease. Current data has supported that ustekinumab provides a highly efficacious treatment option in patients with PsA, especially dactylitis, enthesitis, or severe skin involvement[2]. According to the recent European League Against Rheumatism 2019 recommendation for management of PsA, ustekinumab should be considered particularly in patients with extensive skin involvement who have had an inadequate response to at least one conventional synthetic disease-modifying antirheumatic drug[3]. The efficacy and safety of ustekinumab for the treatment of PsA have been confirmed by phase II and phase III clinical trials[4, 5].

Flare of pustular psoriasis is the most frequently reported paradoxical reaction in patients treated with ustekinumab[1, 6]. However, new-onset vitiligo following treatment of ustekinumab has been described in only 3 cases other than PsA so far[7]. Interestingly, vitiligo itself has also been reported to be treated with ustekinumab in patients with concomitant psoriasis, and alopecia areata[8]. Despite the fact that the pathogenesis of paradoxical reactions is not fully understood yet, in our patient, the development of vitiligo following ustekinumab therapy may be explained by a cytokine imbalance or increased IFN-driven immune response

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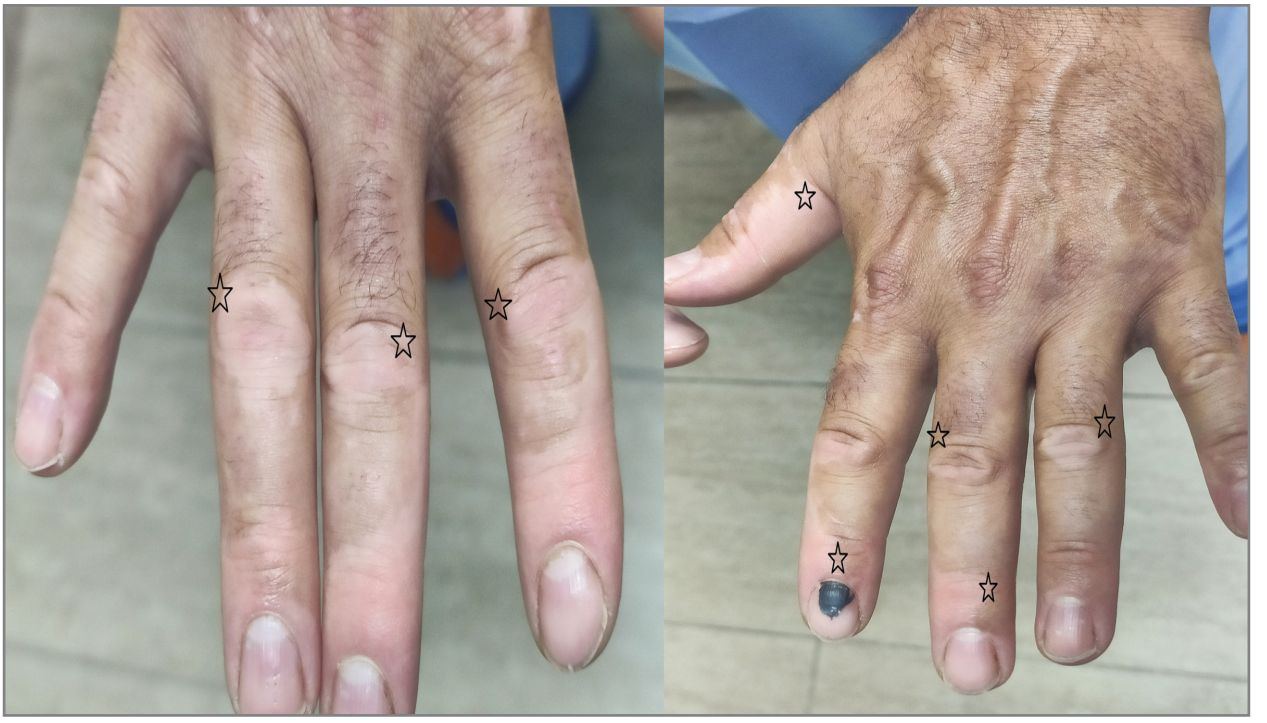

FIGURE 1. Patient at week 16 of ustekinumab therapy with hypopigmented areas on the dorsum of fingers.

predisposing to autoimmune manifestations[9].

There is no consensus on whether the biological agent should be discontinued after developing new-onset vitiligo in patients with rheumatic disease. However, switching to another agent may be a valuable treatment option due the fact that vitiligo may negatively affect patients' self-esteem, personal and social interactions, as well as quality of life[10]. The treatment decision should be made individually by considering the disease activity and severity of vitiligo through shared decision-making between the patient and the physician. In our patient, ustekinumab was discontinued and adalimumab (40 mg every other week) was started. After three months of therapy, the extent and distribution of vitiligo were not increased and the clinical features of PsA are well controlled.

In closing, by presenting this exceptional event, we would like to point out that new-onset vitiligo under ustekinumab therapy may be considered as a new and undescribed paradoxical cutaneous reaction in patients with PsA. Further studies and additional cases are required to decide the appropriate treatment approach and to explain the complete immunopathogenesis behind paradoxical autoimmune reactions during the treatment of ustekinumab and other biologic agents.

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