Accepted Article

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Article type : Letter to Editor

Title: Polyenthesitis during treatment with dupilumab for atopic dermatitis

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Key Word: dupilumab, atopic dermatitis, enthesitis, psoriatic arthritis, ultrasound, IL-4 signaling

Word counts: 600 words

Tables: none

Figures: 2 figures

Conflict of interest disclosure: None declared (for each co-author)

Funding sources: None

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/JDV.16239

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Dear Editor,

Dupilumab is a monoclonal antibody against interleukin-4 (IL-4) receptor that inhibits IL-4 and IL-13 signaling, which plays a central role in type 2 inflammation in atopic dermatitis (AD) (1). Although dupilumab exerts significant therapeutic effects for AD, it occasionally causes some unexpected side effects including conjunctivitis (2), psoriasis (3), and polyenthesitis (4, 5). Here we report the first Asian case of polyenthesitis during the treatment with dupilumab.

A 54-year-old Japanese man who was diagnosed with AD more than 2 years before was started on dupilumab therapy. He was previously treated with oral prednisolone (10 mg/day) and topical steroid, but his skin symptoms were not controlled well (Eczema area and severity index (EASI) 21.6). Shortly after the dupilumab initiation, his skin lesions dramatically improved (EASI 1.5 at week 8) and oral prednisolone was finally weaned off 8 months later (Fig. 1). However, 2 months after the initiation of dupilumab, the patient began to feel pain in bilateral distal and proximal interphalangeal joints, elbows, knees, left shoulder and ankle. He had no history of musculoskeletal or rheumatic diseases. Rheumatoid factor and anti-cyclic citrullinated peptide (anti-CCP) antibody in serum were negative. X-rays of hands and knees showed no remarkable changes on the bones. However, ultrasound showed enthesitis findings at the lateral epicondyle of the bilateral humeri and the patellar tendons (Fig. 2). No significant Doppler signals were

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observed at Achilles tendons. We diagnosed him with polyenthesitis, possibly associated with dupilumab. Because of the therapeutic effects for skin lesions, the patient chose to continue dupilumab treatment, so we continued dupilumab and started celecoxib for the enthesitis, but the pain continued. Therefore, we added treatment with methotrexate, and the symptom got partially improved .

To date, four cases with enthesopathy or arthralgia in AD patients during dupilumab therapy have been reported from the UK (4) and the Netherlands (5). In the first report (4), the authors presented three cases of enthesitis with seronegative arthropathy confirmed by ultrasound. All the three cases developed enthesitis within 16 weeks of dupilumab initiation. In the other report (5), a patient had polyarthralgia 4 weeks after starting dupilumab, although the enthesitis was not evaluated by ultrasound. In our case, the patient showed arthralgia 8 weeks after the initiation of dupilumab, and ultrasound showed typical features of enthesitis (6). Thus, arthralgia associated with dupilumab, possibly due to enthesitis, may generally occur during the first 16 weeks of treatment.

Regarding the treatment of arthralgia, in previously reported four cases, three of them discontinued dupilumab, and only one case led to the improvement of arthralgia. Two of the cases were further treated with non-steroidal anti-inflammatory drugs (NSAIDs) or oral prednisolone. The other one case was treated with NSAIDs under the treatment with dupilumab with poor improvement. In our case, arthralgia was partially improved by methotrexate. When NSAIDs is ineffective, methotrexate may be an option for the treatment of arthralgia during dupilumab.

The etiology of enthesitis associated with dupilumab remains unclear; however, dupilumab may induce enthesitis by enhancing T_H17 cell-mediated inflammation, because enthesitis is a typical feature of spondyloarthritis/psoriatic arthritis, a Th17-mediated inflammation. In fact, development of psoriasis, a Th17-mediated inflammatory skin disease, under treatment with

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dupilumab has been reported (3). A recent study also demonstrates that IL-4 abrogates Th17-mediated inflammation by inhibiting IL-23 production in antigen-presenting cells (7). Thus, blockade of IL-4/IL13 signaling by dupilumab may induce Th17-dominant inflammation in the skin or joint in some cases.

To the best of our knowledge, this is the first report of polyenthesitis during dupilumab treatment in Asia. Close attention should be paid to unexpected side effects, including polyenthesitis, during the treatment with dupilumab.

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Figure legends

Figure 1

Clinical findings.

(A) Before dupilumab treatment.

(B) Eight months after the initiation of dupilumab.

Figure 2

Ultrasound findings ten months after dupilumab therapy.

(A) Lateral epicondyle of the right humerus. Longitudinal scan. Doppler signals at the tendon insertion site is shown.

(B) Right distal patellar enthesis. Longitudinal scan. The patellar tendon is hypoechoic and thickened, with Doppler signals at the enthesis is represented.

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Figure 1

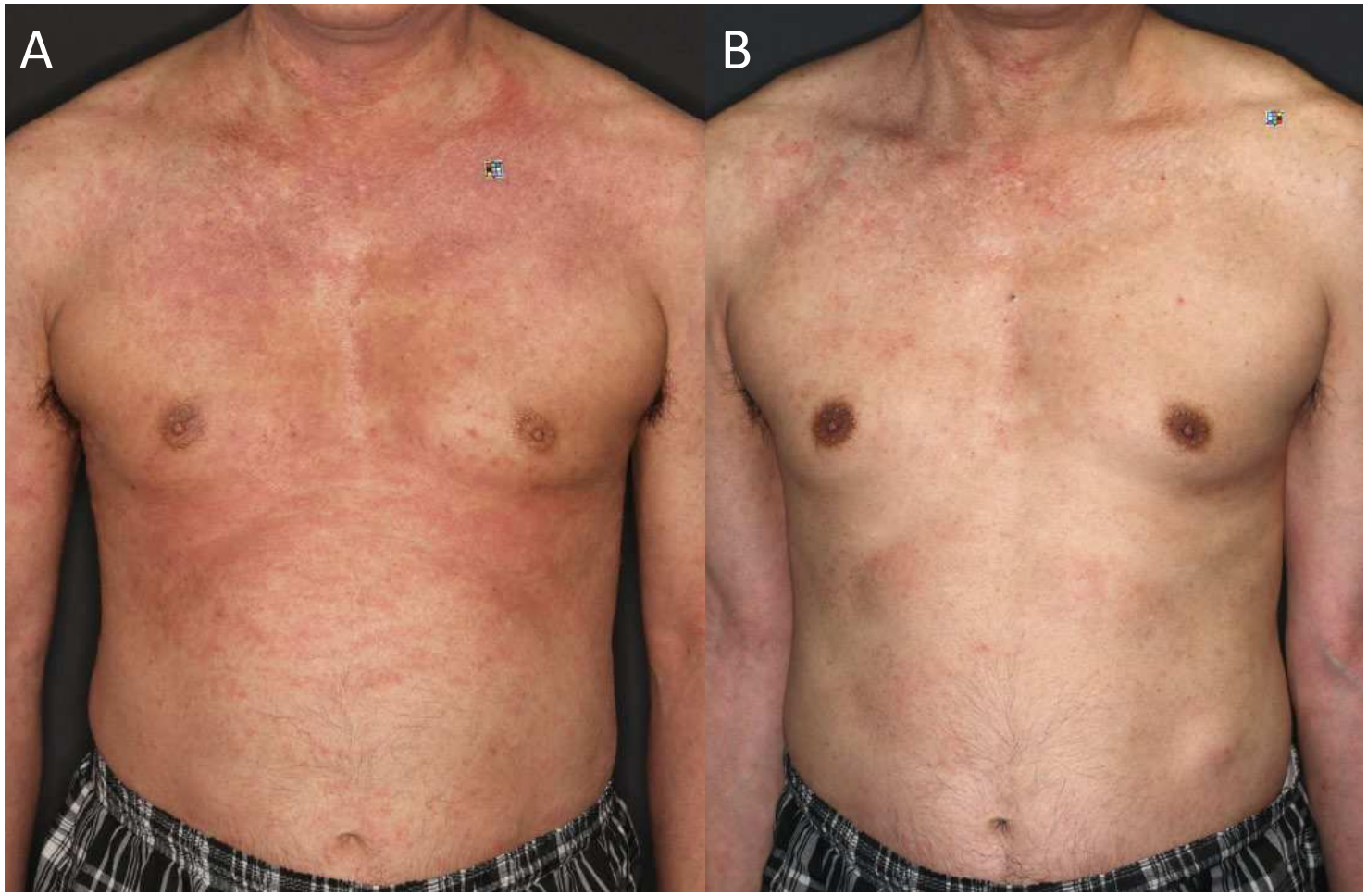

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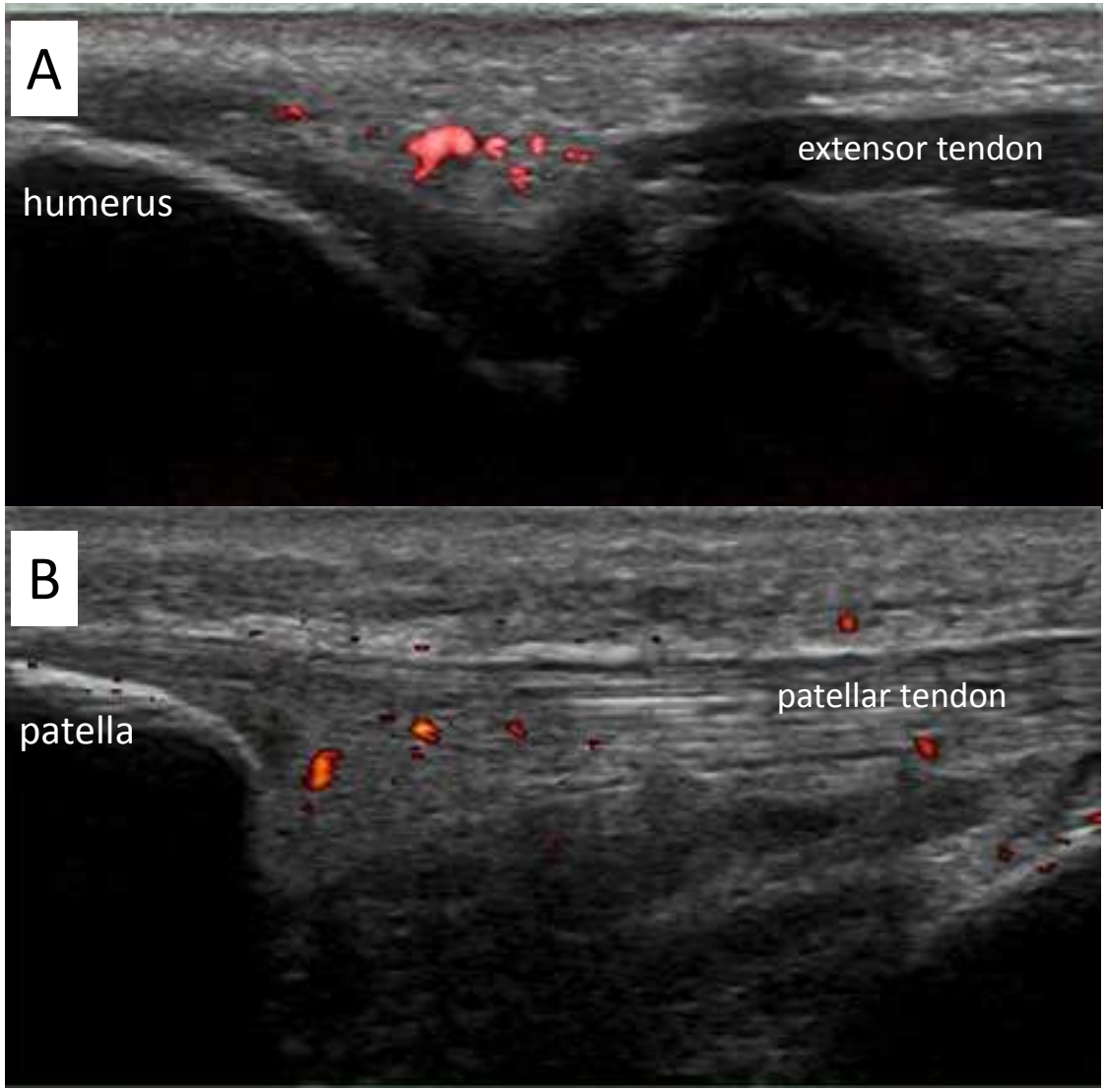
Figure 2

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