Resolution of accelerated nodulosis with upadacitinib in a patient with systemic lupus erythematosus and Jaccoud's arthropathy

Sirs,

The patient is a 38-year-old woman with a longstanding history of systemic lupus erythematosus (SLE) previously manifested with hand arthralgias, photosensitivity, malar rash and Raynaud's. She presented with subcutaneous nodules on the hands after 11 months of treatment with oral methotrexate (MTX) for metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joint pain.

Physical examination revealed numerous small (<4 mm) nodules over the extensor digitorum tendon sheaths in both hands (Fig. 1A, left). Laboratory findings showed positive antinuclear antibodies [(ANA) 1/640, speckled pattern], antiribonucleoprotein (RNP), anti-Smith (SM), and anti-chromatin antibodies, with negative double-stranded DNA antibodies (anti-dsDNA) [0 U/ml (normal 0-14 U/ml)]. Rheumatoid factor (RF) and anti-CCP antibodies were negative. Complement C3 and C4 levels were unremarkable. X-ray of hands showed subluxations in MCP and PIP joints without erosions (Jaccoud's arthropathy). Biopsy of the right ring finger subcutaneous nodule showed superficial and deep granulomatous dermatitis with necrosis and hyalinisation of dermal collagen (necrobiosis) suggestive of a rheumatoid nodule (Fig. 1B, right, 40 x magnification, haematoxylin & eosin stained, arrows mark areas of necrobiosis). The patient was diagnosed with MTX-induced accelerated nodulosis (1) and MTX was gradually discontinued. MTX discontinuation resulted in reduction in the size and numbers of subcutaneous nodules. When her arthritis flared, she was started on low dose of oral leflunomide (LEF). After up-titrating the dose of LEF to control her arthritis, there was exacerbation of subcutaneous nodules in the hands and appearance of a new one in the extensor surface of the right elbow. LEF was discontinued, and she was switched to oral upadacitinib for worsening hand synovitis. Upadacitinib treatment resulted in remission of her arthritis and resolution of the subcutaneous nodules few months later.

This case is unusual in that MTX induced nodules developed in a patient with SLE that was treated for Jaccoud's arthropathy. MTX-induced nodules are most commonly associated with seropositive rheumatoid arthritis and may arise from increased adenosine release from infiltrating macrophages in the extra-articular tissue and enhanced adenosine A1 receptor signalling promoting multinucleated giant cell formation and nodule formation (2). Exacerbation of accelerated nodulosis by leflunomide has been described in the literature, but the mechanism is unknown (3).

Although lupus panniculitis was initially considered in the differential diagnosis for the nodules, clinical presentation was atypical as lupus panniculitis usually affects the lateral aspects of the arms and shoulders, thighs, buttocks, trunk, face, and scalp. Since biopsy findings were consistent with a rheumatoid nodule rather than the lymphocytic panniculitis, hyaline papillary bodies, and lymphoid nodules in the dermis and subcutaneous tissue seen in lupus panniculitis (4), we believe that her nodules were drug-induced.

Our case is noteworthy because upadacitinib, a selective JAK1 inhibitor, facilitated the resolution of the subcutaneous nodules. Although, there is no direct evidence that updacitinib resulted in the treatment of the nodules, emerging clinical data suggest the efficacy of Janus Kinase (JAK) inhibitors not only in arthritis in patients with SLE (5,6), but also in treatment of granuloma annulare (7, 8) that is another type of granulomatous dermatitis. The mechanism needs to be yet explored but JAK inhibitors could be suggested as a treatment option for MTX and LEF induced accelerated nodulosis.

D. Michailidou[1], *MD, PhD*
T.H. Long[2], *MD*
Z.B. Argenyi[2], *MD*
E.H. Noss[1], *MD, PhD*

[1]Division of Rheumatology, [2]Department of Pathology, University of Washington, Seattle, WA, USA.

Please address correspondence to:
Despina Michailidou
Division of Rheumatology,
Department of Medicine,
University of Washington,
1959 NE Pacific Street
Seattle, WA 98195 USA.
E-mail: despina1@uw.edu

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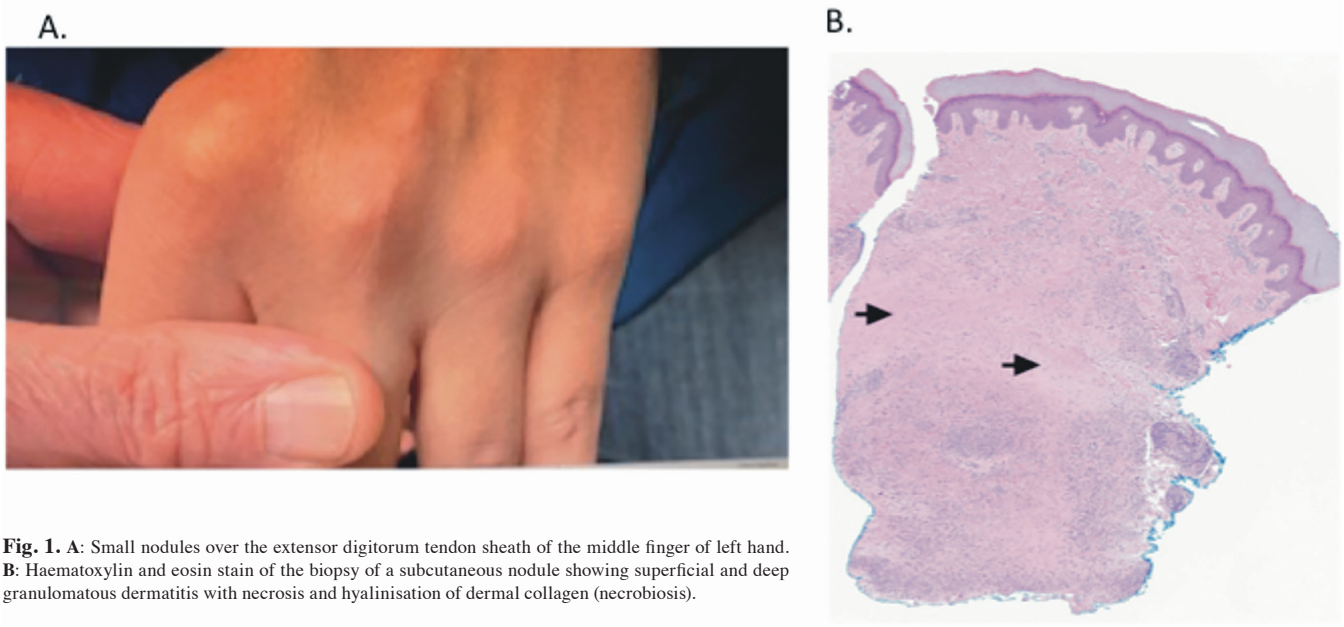

Fig. 1. **A**: Small nodules over the extensor digitorum tendon sheath of the middle finger of left hand. **B**: Haematoxylin and eosin stain of the biopsy of a subcutaneous nodule showing superficial and deep granulomatous dermatitis with necrosis and hyalinisation of dermal collagen (necrobiosis).

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