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Reply

To the Editor:

We thank Drs. Pollard and Kono for their comments. Our work demonstrated a requirement for caspase 1 in the induction of a lupus phenotype following exposure to pristane. Drs. Pollard and Kono propose the concept that innate immune pathways required to induce autoimmunity in models of spontaneous or induced immune disease may exhibit variability, emphasizing the complexity of autoimmunity development. As Drs. Pollard and Kono report, *Nlrp3* and *Casp1* are not required for autoantibody development after exposure to mercury (1). However, they do note a reduction in renal immune deposits in caspase 1–deficient mice. This finding may reflect 2 separate roles for the inflammasome in disease development: nephritis induction in most models and inhibition of autoimmunity in some models. This variability in phenotype depending on the specific strain or model studied is not specific to inflammasome-related pathways and has been well described in other innate pathways, including type I interferons and others (2–6), and describes the complexity of studying lupus and autoimmunity in murine systems.

Nevertheless, it has now been shown in both genetically prone mice and in a murine model of induced lupus that the inflammasome may be implicated in lupus pathogenesis (7). This also applies in the specific case of lupus nephritis (8–11) and may indicate crucial priming events at the tissue level mediated by interleukin-1β and/or interleukin-18 (11–13). Certainly, renal macrophages appear to be important pathogenic mediators and may serve as an essential source of inflammasome activation in the kidneys (10,14–16).

Unlike mercury-induced autoimmunity, in the pristane-induced model of autoimmunity, caspase 1 is required for prolongation of the type I interferon response and autoantibody development. The differences between administration of mercury and administration of pristane may be reflected in the hyperinflammatory response following pristane exposure, in strain-specific differences, or in different requirements for phenotypic manifestations in various autoimmune diseases. Because cell death in response to pristane is diminished in caspase 1–deficient BALB/c mice, it is possible that caspase 1 protects against autoantigen exposure and induction of Toll-like receptor ligands, which are required for the development of pristane-induced lupus (17).

Further research into the effects of caspase 1 on autoantibody development in the pristane-induced model of autoimmunity and in mice with a genetic predisposition to lupus may shed additional light on the role of this protein and that of the inflammasome machinery in autoimmune disease.

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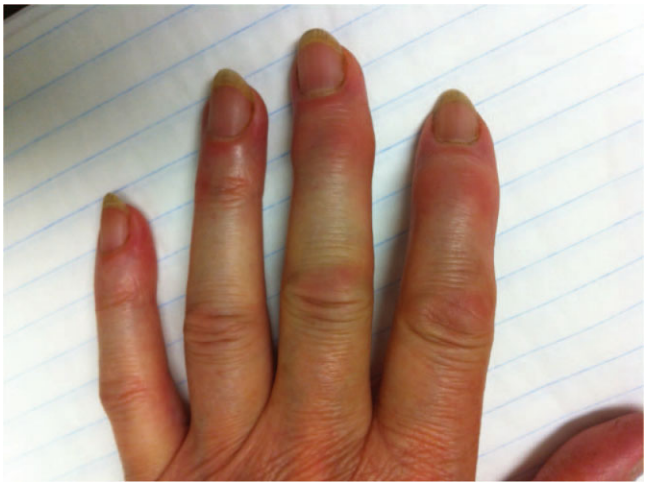
Clinical Image: Painful swollen distal interphalangeal joints are not always Heberden's nodes!



The patient, a 71-year-old woman, presented to our clinic with a 2-month history of tenderness and swelling at multiple distal interphalangeal (DIP) joints, both wrists, and both knees. No skin or nail lesions were observed, and her family history did not reveal psoriasis. The rheumatoid factor value was 246 IU/ml (normal <15 IU/ml), the anti–cyclic citrullinated peptide antibody level was >340 units/ml (normal <10 units/ml), the erythrocyte sedimentation rate was 36 mm/hour (normal 0–28 mm/hour), and the C-reactive protein level was 43.9 mg/liter (normal <10.0 mg/liter). Radiography did not show erosions or osteoarthritis of the small finger joints. Hence, a diagnosis of rheumatoid arthritis (RA) was made. Despite treatment with subcutaneous methotrexate at a dosage of up to 20 mg/week and subsequent treatment with subcutaneous golimumab, disease remained active while the patient received prednisone dosages of >15 mg/day. A few weeks after the initiation of tocilizumab treatment at a dosage of 8 mg/kg every 4 weeks, the patient reported significant pain relief, and synovitis of the DIP joints disappeared. RA frequently involves the small joints of the hands and feet; in textbooks, the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints are typically described as being affected. Indeed, the prevalence of MCP and PIP joint involvement in RA is high. DIP joint involvement, as in our patient, is less frequently seen, but still has a prevalence of up to 10% (Ichikawa N, Taniguchi A, Kobayashi S, Yamanaka H. Performance of hands and feet radiographs in differentiation of psoriatic arthritis from rheumatoid arthritis. Int J Rheum Dis 2012;15:462–7). This clinical case reminds us that despite the classic notion of RA affecting the more proximal finger joints, patients with RA can also present with arthritis predominantly of the DIP joints. Therefore, swelling and pain of the DIP joints in elderly individuals are not always due to Heberden's nodes.

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