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A novel animal model of aromatase inhibitor induced arthralgia suggests that the pathological mechanism of inflammation is estrogen-independent

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Aromatase Inhibitors (AIs) block estrogen production and significantly improve overall survival rates of post-menopausal breast cancer patients by reducing tumor recurrences. However, half of patients taking these drugs develop aromatase inhibitor induced arthralgia (AIIA), which is characterized by severe pain and inflammation in various joints. Since AIIA leads to suspension of therapy in 20% of patients, reducing incidence may provide sustained AI treatment and enhanced long-term survival. To establish a novel animal model of this autoimmune-mediated inflammatory disease, female BALB/C-Tg(NFκB-RE-luc)-Xen mice, which carry a luciferase reporter gene under the regulation of κB-responsive sites, were oophorectomized and treated with AI (letrozole) by daily subcutaneous injection. In vivo bioluminescent imaging revealed significantly enhanced NFκB activation in the hind limbs compared to oophorectomized controls receiving vehicle treatment and analysis of knee joints and legs by micro-MRI imaging showed enhanced signal detection in the joint space and surrounding tissue following AI treatment. Surprisingly, enhanced MRI detection was also demonstrated in non-oophorectomized mice that were treated with AI. Histopathological analysis demonstrated mild inflammation in the synovial tissue and joint damage in mice treated receiving AI both with and without oophorectomy. Tenosynovitis and inflammatory muscle tissue infiltrates were detected in AI-treated mice, which correlated with significant elevation of IL-2, IL-4, IL-6, and CXCL1. Collectively, these data establish a novel mouse model of AIIA and suggest that the pathogenesis of AI-induced inflammation is estrogen-independent. Future studies will characterize this inflammatory mechanism to provide insight into potential therapeutic strategies to mitigate this inflammatory burden.

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