ARP Rheumatology 2025;4:317-319
https://doi.org/10.63032/HZSJ4098

LETTERS TO THE EDITOR

# Upadacitinib in rheumatoid nodules: beyond joint control

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Dear Editor,

Rheumatoid nodules (RN) are a common extra-articular manifestation in rheumatoid arthritis (RA), occurring in up to 30% of patients, and are associated with more severe disease and high-titer rheumatoid factor (RF) and/or anti-cyclic citrullinated peptide antibodies (ACPA) positivity. They most commonly occur on pressure areas, including elbows, finger joints, or occasionally in internal organs such as the lungs[1,2]. RN may be refractory to disease-modifying antirheumatic drugs (DMARDs) and can paradoxically worsen with methotrexate or leflunomide despite improvement in joint disease activity[3]. Although often asymptomatic, RN may cause pain, functional or aesthetic impairment, and in the lungs, cavitation may lead to complications such as hemoptysis, pleural effusion, or pneumothorax. Their management remains challenging, as evidence of regression with standard RA therapies is limited. However, small case series have suggested that Janus kinase (JAK) inhibitors (JAKi) may be effective in RN treatment, including those affecting the skin and lungs[4-9]. In this context, we report two cases of RN that markedly improved following treatment with upadacitinib.

The first case concerns a 50-year-old male smoker with recent-onset erosive, seropositive RA (RF and ACPA positive) who developed multiple subcutaneous nodules over the extensor surfaces of the elbows and wrists, leading to severe functional impairment. Because of active hepatitis C virus infection with elevated liver enzymes, sulfasalazine was initiated as first-line therapy, with inadequate arthritis control. After successful antiviral treatment, methotrexate was tried, but RN increased in number and size (the largest measuring 7 cm in diameter). Given this paradoxical progression, methotrexate was discontinued and upadacitinib 15 mg/day was initiated. Four months after treatment, there was >50% reduction in nodule size and complete arthritis resolution.

The second case concerns a 64-year-old woman with seropositive RA of 10 years' duration, who had a history of inadequate response to multiple DMARDs, including methotrexate, sulfasalazine, hydroxychloroquine, tofacitinib and finally tocilizumab in addition to leflunomide. Although she initially responded to tocilizumab and leflunomide, she subsequently experienced a progressive loss of treatment efficacy. Concurrently, she developed a gradually worsening dry cough, prompting a chest computed tomography (CT) scan. The CT revealed multiple bilateral cavitary subpleural nodules, located adjacent to the hilum and bronchi. Fluorodeoxyglucose F-18 positron emission tomography showed mildly increased, nonspecific metabolic activity with standardized uptake values ranging from 1 to 3. A biopsy from a lesion in the left upper lobe demonstrated necrotizing granulomas with palisading histiocytes, findings that were compatible with either tuberculosis infection or RN. However, microbiological tests were negative for tuberculosis. The absence of lesion progression over the course of one year, as confirmed by serial CT scans, supported the diagnosis of pulmonary RN. Given the failure of tocilizumab plus leflunomide to control her joint disease, treatment was switched to upadacitinib 15 mg daily alongside leflunomide 10 mg daily. This regimen resulted in improvement of the pulmonary RN after six months (Figure 1) and achievement of clinical remission.

These cases highlight the difficulty of managing RN, particularly when paradoxically induced or aggravated by DMARDs. Diagnosis can also be challenging, especially in the lungs, where imaging and histology may not distinguish malignancy or infection such as tuberculosis. In the second case, while leflunomide may have contributed to the development of RN, it is notable that adding upadacitinib successfully controlled the RN without requiring discontinuation of leflunomide. Furthermore, this case underscores the possibility of pulmonary RN occurring in the absence of cutaneous nodules.

Our findings add to growing evidence suggesting that JAK inhibition may offer benefits beyond joint control in RA. Their potential for monotherapy is also advantageous. The mechanism underlying nodule re-

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**Submitted:** 02/11/2025
**Accepted:** 08/12/2025

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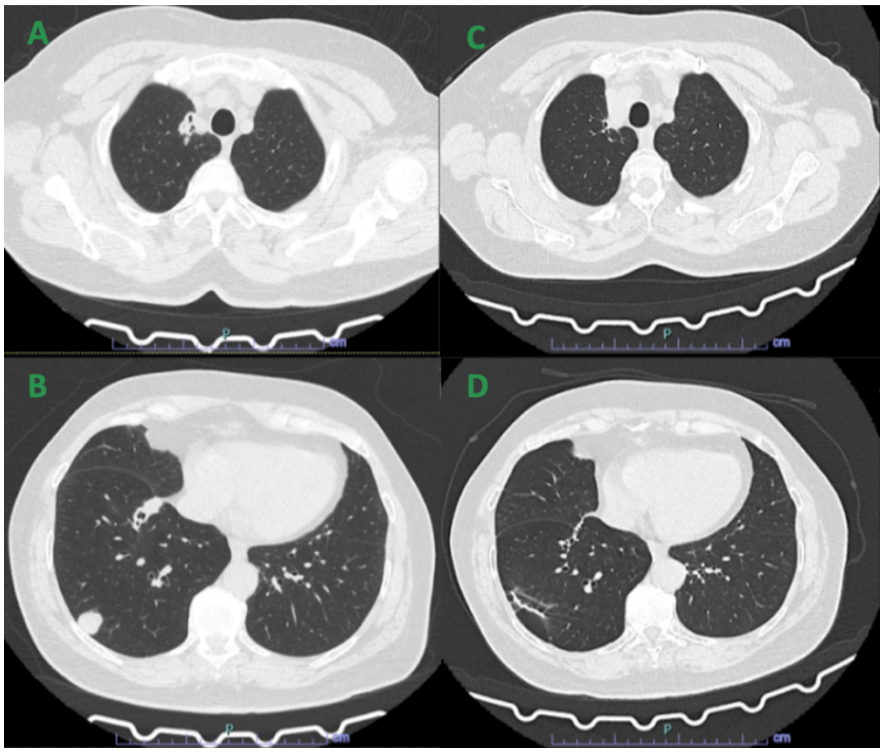


**Figure 1.** High-resolution chest computed tomography (CT) scan showing a reduction in the size of subpleural and parenchymal rheumatoid nodules, along with bronchiectasis, comparing the initial CT (images A and B) with the follow-up scan six months after initiation of upadacitinib therapy (images C and D) in patient 2.

gression remains speculative; however, given the efficacy and rapid onset of JAKi in reducing RN size, the JAK/STAT pathway is likely involved. It is also hypothesized that JAK inhibition modulates granulomatous inflammation, supported by reports of efficacy in granulomatous disorders such as sarcoidosis[10]. Our findings further support emerging data on JAK inhibitor efficacy in controlling rheumatoid nodules[4–9].

In summary, upadacitinib led to significant regression of cutaneous and pulmonary RN in two patients with refractory seropositive RA, with complete articular remission. Although anecdotal, these observations underscore the potential of JAK inhibitors as a therapeutic option for difficult-to-treat rheumatoid nodules. Further studies are warranted to confirm these findings.

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## SUPPLEMENTARY MATERIAL

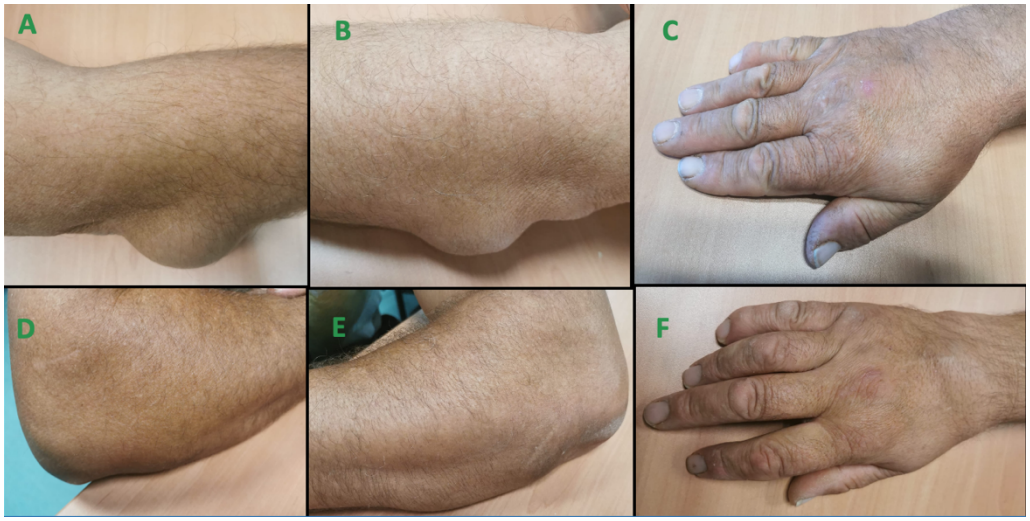


**Figure 2.** Rheumatoid nodules on the extensor surfaces of the right and left elbows and the right wrist in patient 1, before (images A–C) and a >50% reduction in nodule size four months after initiation of upadacitinib treatment (images D–F).