

## Granulomatous disease and the two faces of Janus: divergent effects of tofacitinib therapy for inflammatory arthritis

Sirs,

Janus kinases (JAKs) are intracellular tyrosine kinases utilised for signalling by extracellular receptors involved in many pro-inflammatory pathways like interferon- $\gamma$  (1) and some anti-inflammatory pathways like interleukin-10 (2). JAK-inhibitors, already approved for various inflammatory conditions including rheumatoid arthritis (RA), also show promise for treating sarcoidosis (3, 4). This communication contrasts two novel cases of patients treated with the JAK-inhibitor tofacitinib: a woman with RA developing granulomatous hepatitis during therapy and a man with intractable arthropathic and cutaneous sarcoidosis responding to treatment.

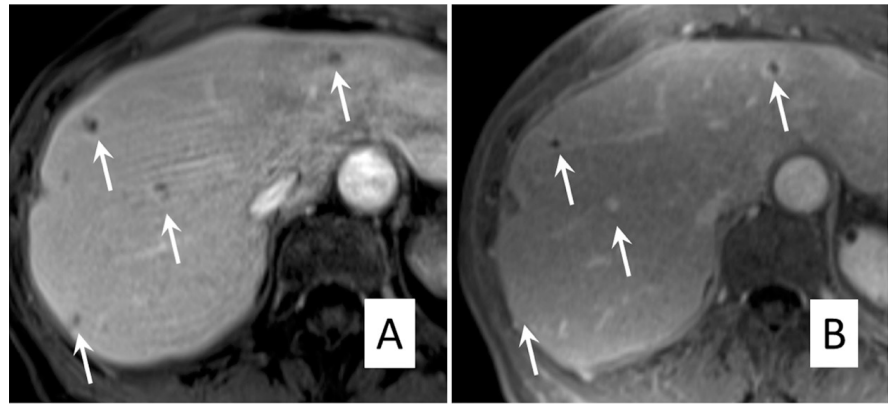
Patient 1 is a woman with erosive RA since the age of 44. Methotrexate, gold, hydroxychloroquine, sulfasalazine, azathioprine, leflunomide, etanercept, abatacept, and rituximab were ineffective. Infliximab and subsequently adalimumab were effective but failed increasingly corticosteroid-dependent, requiring at least prednisone 10 mg daily. At the age of 67, tofacitinib 5 mg twice daily was started, resulting in steady clinical improvement.

After thirteen months of durable response, magnetic resonance imaging (MRI) for unrelated monitoring of renal cysts incidentally revealed multiple hypo-enhancing hepatic masses unseen prior to tofacitinib therapy (Fig. 1A). The patient was asymptomatic; liver enzyme tests were normal. Liver biopsy revealed non-necrotising and necrotising granulomatous inflammation (Fig. 2). Stains and cultures for acid-fast bacilli and fungi were negative.

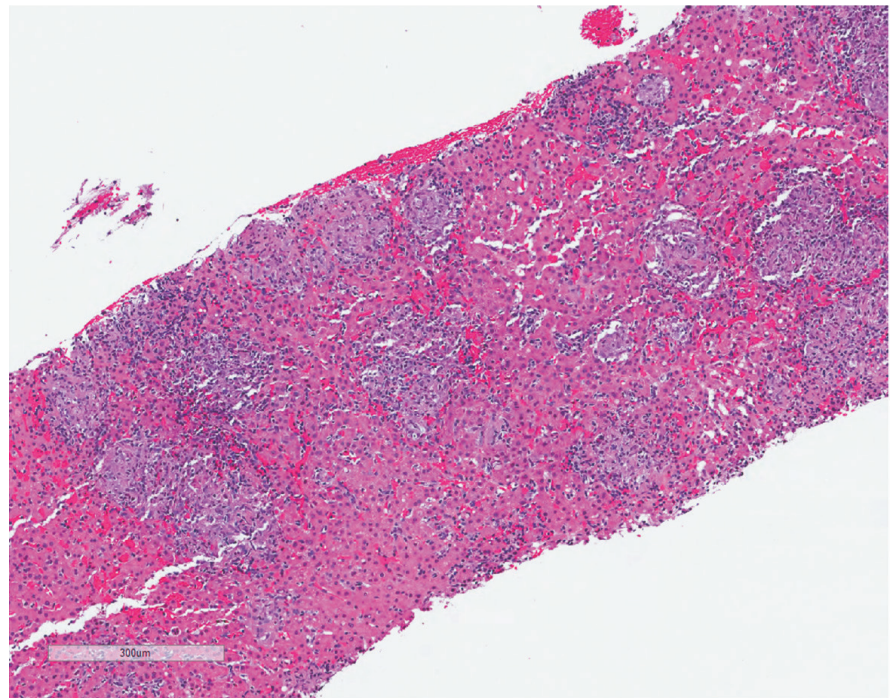
Tofacitinib was discontinued, and the patient was monitored without intervention. MRI after three months showed disappearance or shrinkage of the lesions (Fig. 1B). Serial MRI showed further resolution, 33 months after drug cessation.

Patient 2 is a man with bilateral hilar and mediastinal lymphadenopathy incidentally noted at the age of 28; biopsy had been deferred because the radiology was stereotypical of sarcoidosis. He remained asymptomatic and untreated until he developed skin lesions and inflammatory polyarthritis at the age of 47. Skin biopsy demonstrated non-caseating granulomas; stains for acid-fast bacilli and fungi were negative. Rheumatoid factor and anti-cyclic citrullinated antibodies were negative.

Hydroxychloroquine, methotrexate, leflunomide, infliximab, adalimumab, and abatacept were ineffective. Methylpredni-



**Fig. 1.** Contrast enhanced MRI of the liver (A) showing multiple hypo-enhancing lesions (white arrows). All lesions have either disappeared or decreased in size within three months after discontinuation of tofacitinib (B).



**Fig. 2.** Core biopsy of the liver shows numerous granulomas, characterised by nearly spherical aggregations of epithelioid histiocytes accompanied by lymphocytes and occasional multinucleated giant cells (H&E).

solone 16 mg daily barely controlled his disease and resulted in myopathy, osteoporotic fractures, and hip osteonecrosis. Frequent large-volume arthrocenteses with corticosteroid injections of his knees were required.

Tofacitinib 5 mg twice daily was initiated. Within weeks, the polyarthritis was markedly improved. The skin disease resolved completely. Over the ensuing year, corticosteroid requirements significantly decreased, and no further arthrocenteses were required. Patient 2 is the first report of sarcoid arthropathy responsive to tofacitinib, reaffirming benefit of JAK-inhibitors in sarcoidosis (3, 4). JAK-mediated interferon- $\gamma$  pathways are implicated in granuloma formation (5), and so the therapeutic potential of JAK-inhibitors is unsurprising. Unexpected, however, especially amidst recent

demonstration of impressive tofacitinib-induced dissolution of sarcoid granulomas (3), is the unprecedented paradoxical tofacitinib-induced granulomatous inflammation in patient 1.

Small molecules generically might induce granulomatous hepatitis via hapten formation with macromolecules (6). Tofacitinib, however, may paradoxically promote inflammatory processes via its mechanistic effects. JAKs are aptly named for the two-faced Roman god Janus because they possess two nearly identical domains with opposing functions: a signalling kinase domain which is the target for tofacitinib inhibition and an inert pseudokinase domain that downregulates the kinase (7, 8). Perhaps under certain conditions, tofacitinib interferes with pseudokinase function, thereby disinhibiting the kinase and promot-

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ing immune activation. This draws analogy to JAK2 pseudokinase mutations resulting in unregulated constitutive JAK2 kinase activity (9).

JAK inhibition might also cause net pro-inflammatory effects in certain immunologic milieus by preferentially suppressing JAK-mediated anti-inflammatory cytokines such as interleukin-10, known to impair granuloma maturation (10). Accordingly, disproportionate suppression of interleukin-10 activity by JAK-inhibitors may promote granulomatous inflammation.

Going forth, it will be intriguing to observe whether granulomatous inflammation is a common adverse effect of JAK-inhibitors, whether it is a drug class effect, and whether JAK subtype specificity of individual agents is determinant.

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The author expresses his gratitude to Dr Douglas Mintz and Dr Thomas Bauer for their thoughtful discussions and insights with radiologic and pathologic findings.

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### References

1. O'SHEA JJ, HOLLAND SM, STAUDT LM: JAKs and STATs in immunity, immunodeficiency, and cancer. *N Engl J Med* 2013; 368: 161-70.
2. RILEY JK, TAKEDA K, AKIRA S, SCHREIBER RD: Interleukin-10 receptor signaling through the JAK-STATp: Requirement for two distinct receptor-derived signals for anti-inflammatory action. *J Biol Chem* 1999; 274: 16513-21.
3. DAMSKY W, THAKRAL D, EMEAGWALI N, GALAN A, KING B: Tofacitinib treatment and molecular analysis of cutaneous sarcoidosis. *N Engl J Med* 2018; 379: 2540-6.

4. SEJOURNET L, KODJIKIAN L, GRANGE L, GRUMET P, JAMILLOUX Y, SEVE P: Resolution of ocular and mediastinal sarcoidosis after Janus kinase inhibitor therapy for concomitant rheumatoid arthritis. *Clin Exp Rheumatol* 2021; 39: 225-6.
5. ROSENBAUM JT, PASADHIKA S, CROUSER ED *et al.*: Hypothesis: Sarcoidosis is a STAT1-mediated disease. *Clin Immunol* 2009; 132: 1794-83.
6. MCMASTER KR, HENNIGAR GR: Drug-induced granulomatous hepatitis. *Lab Invest* 1981; 44: 61-73.
7. CHRENCIK JE, PATNY A, LEUNG IK *et al.*: Structural and thermodynamic characterization of the TYK2 and JAK3 kinase domains in complex with CP-690550 and CMP-6. *J Mol Biol* 2010; 400: 413-33.
8. HAMMARÉN HM, VIRTANEN AT, RAIVOLA J, SILVENNOINEN O: The regulation of JAKs in cytokine signaling and its breakdown in disease. *Cytokine* 2019; 118: 48-63.
9. CONSTANTINESCU SN, LEROY E, GRYSHKOVA V, PECQUET C, DUSA A: Activating Janus kinase pseudokinase domain mutations in myeloproliferative and other blood cancers. *Biochem Soc Trans*. 2013; 41: 1048-54.
10. CYKTOR JC, CARRUTHERS B, KOMINSKY RA, BEAMER GL, STROMBERG P, TURNER J: IL-10 inhibits mature fibrotic granuloma formation during Mycobacterium tuberculosis infection. *J Immunol* 2013; 190: 2778-90.