1C and D). Strikingly, the patient’s CD16hi subset declined from 22 to 6.8% 2 weeks following his first infusion of infliximab 5 mg/kg (Fig. 1E) and remained at 6.6% after the second infliximab infusion (data not shown).

Macrophages derived from our patient secreted high levels of IP-10, which declined to near control levels post-infliximab (Fig. 1F). RANTES displayed a similar pattern, but neither IL-12 nor IL-23 was detected in patient or control samples (data not shown).

To our knowledge, this is the first attempt to assess the response of monocyte/macrophage activation to anti-TNF-α therapy of sarcoidosis. A patient with life-threatening sarcoid exhibited increased monocyte/macrophage activity that normalized shortly after clinically successful TNF-α blockade. The findings implicate systemic monocyte activation in the pathophysiology of sarcoidosis and suggest that monocyte activation is maintained by TNF-α in vivo. Monocyte activation markers may thus be useful as a biomarker of therapeutic efficacy in this setting. Further study is required to establish whether these biomarkers correlate with disease activity in sarcoid specifically, or in all granulomatous conditions, and whether these or other activation phenotypes could report on (re)activation of intracellular microbial infection post-TNF-α blockade.

Our patient defied expectations by surviving, and continuing in part-time employment, for ~2 years after the institution of infliximab. He died as a result of a chest infection and secondary pulmonary arterial hypertension, complicating established pulmonary disease. The post-mortem revealed no evidence of active sarcoidosis.

Rheumatology key message


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Comment on: Usefulness of anti-cyclic citrullinated peptide antibody and rheumatoid factor to detect rheumatoid arthritis in patients with systemic sclerosis

Sir, We read the recent article by Ueda-Hayakawa et al. [1] with great interest. They reported that the frequency of elevated serum MMP-3 levels was significantly higher in patients with dcSSc than in those with lcSSc. They also stated that there was a significant correlation between the MMP-3 level and the modified Rodnan total skin thickness score (mRTSS) in SSC patients. However, their findings contradict the previous report that the TSS is higher in patients with normal MMP-3 levels than in those with elevation of MMP-3 [2]. Further, serum MMP-3 levels are reported to be normal in steroid-free SSC patients [3]. We would like to make some comments about the relationship between the serum level of MMP-3 and SSC.
MMP-3 is one of the reliable biomarkers for evaluating disease activity and joint destruction in RA. It is released from the surface layer of the synovial lining, and contributes to destruction of the cartilage and the joint [4]. However, the specificity of MMP-3 is low and elevated serum levels of MMP-3 occur in many other collagen vascular diseases besides RA [3, 5-7]. For example, MMP-3 levels are increased in SLE patients with kidney involvement, and there is a positive correlation between the MMP-3 level and glucocorticoid (GC) dose [3]. Although the source and the mechanism involved are unclear, GC therapy increases serum levels of MMP-3, as measured with the method used by Ueda-Hayakawa et al. [1]. We have observed an increase in serum MMP-3 levels after GC therapy in patients with a variety of rheumatic diseases besides RA. We compared serum levels of MMP-3 before and after GC therapy (>0.5 mg/kg/day of oral prednisolone with a median dose of 50mg (20–80mg)) in 22 patients (10 men and 12 women) with a median age of 50 (22-79) years and the following diseases: DM in five; SLE, PM, adult-onset Still’s disease, SSC, microscopic polyangiitis and Churg–Strauss syndrome in two each; and TA, MCTD, SS, Behçet’s disease and retroperitoneal fibrosis in one each. Serum MMP-3 levels were measured by SRL (Tachikawa, Tokyo, Japan), using the same assay system as that employed by Ueda-Hayakawa et al. [1]. Before and after commencement of GC therapy, serum MMP-3 was measured at various times [median: 8 (5–12) days]. As a result, the MMP-3 level increased in all of the patients tested (Fig. 1). Even in a healthy individual (T.N.) receiving prednisolone (0.5 mg/kg/day) for 7 days, the serum MMP-3 level increased from 89 to 326 ng/ml after 3 days and then to 339 ng/ml by 1 week later. Also, when only 5 mg/day of prednisolone was administered to T.N. for 7 days, the MMP-3 level increased from 91 to 152 ng/ml in 1 week. The serum MMP-3 level and the GC dose were correlated well in patients whose MMP-3 levels were measured at least twice during their course (data not shown).

Our observations support the report that serum levels of MMP-3 are elevated in various rheumatic diseases and in LN patients on GC [3]. Ueda-Hayakawa et al. [1] did not report the details of treatment (especially GC) or the timing of serum sample collection (at the first visit or during follow-up). Patients with dcSSc might have been treated with GC more frequently for skin sclerosis than those with lcSSc, so that the serum MMP-3 level may be correlated with the GC dose rather than with the mRTSS in dcSSc. In RA patients, serum levels of pro-MMP-3 increase during treatment with prednisone (7.5 mg/day) and then decrease rapidly after stopping prednisone [8]. Another study has also suggested an influence of GC on the serum MMP-3 level in patients with RA [9]. From these findings, it seems likely that even low-dose GC therapy can affect the serum level of MMP-3. Another problem is that Ueda-Hayakawa et al. [1] did not take into account the sex difference in the normal range of MMP-3. The normal serum level of MMP-3 is twice as high in men (<121.0 ng/ml) as in women (<59.7 ng/ml), and the proportion of men was higher among dcSSc than lcSSc patients in Ueda-Hayakawa’s study. In conclusion, MMP-3 levels should be evaluated with caution in patients on GC therapy. The relationship between MMP-3 and mRTSS should be reassessed with consideration of GC therapy and sex.

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References
Comment on: Bone marrow lesions in people with knee osteoarthritis predict progression of disease and joint replacement: a longitudinal study

SIR, We would like to comment on a recently published article investigating the relationship between bone marrow oedema-like lesions (BMLs) and longitudinal change in tibial cartilage volume and subsequent risk of knee joint replacement in subjects with knee OA [1]. BMLs are known to play a role in pain [2] and progression of structural deterioration [3-6] in subjects with knee OA. Thus, selection of adequate MRI pulse sequences that are able to assess the maximum extent of BMLs is crucial for evaluation. Tanamas et al. [1] used a T1-weighted fat-suppressed 3D gradient recall acquisition in the steady state to assess both BMLs and articular cartilage. Gradient recalled echo (GRE)-type sequences, such as the one used by the authors in their study, are insensitive to marrow abnormalities due to trabecular magnetic susceptibility or T2* effects, which may lead to underestimation of BML size [7-9]. Such sequences also demonstrate limited sensitivity in the detection of BMLs when using routine fast spin echo (FSE) sequences as the reference standard [10, 11]. This was summarized and published in a consensus statement by OMERACT and OARSI (OA Research Society International) in 2006 [12]: ‘GRE techniques, even with robust fat suppression or water excitation, are notoriously insensitive to marrow

Fig. 1 Underestimation and lack of sensitivity of T1-weighted fat-suppressed (FS) SPGR sequence in the assessment of BMLs. (A) Sagittal T2-weighted FS image depicts BMLs in the patellofemoral compartment (→) as well as in the proximal tibiofibular joint (●). (B) Sagittal T1-weighted FS SPGR of the same knee obtained just after the acquisition of sagittal T2*-weighted FS sequence shows relevant underestimation of the size of BML in the femoral trochlea (→), as well as lack of sensitivity, as the patellar BML could not be detected in such technique. Note that BMLs in the proximal tibiofibular joint are barely seen in SPGR.