

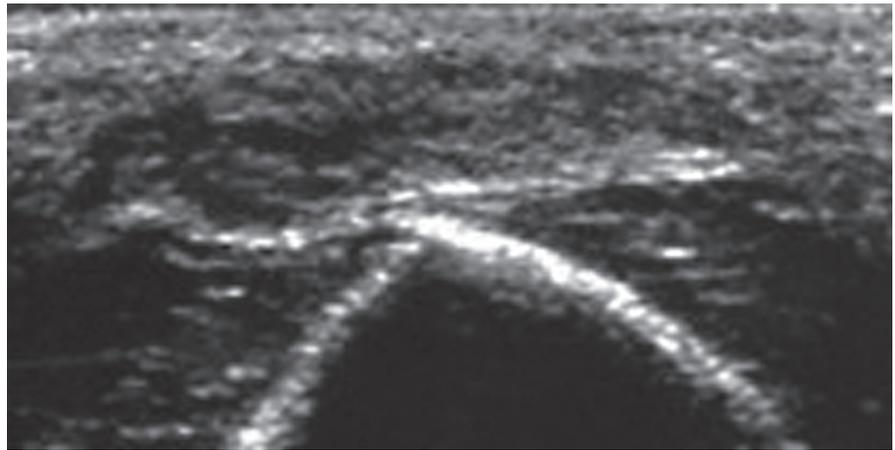
**Appearance of rheumatoid nodules following anti-tumor necrosis factor  $\alpha$  treatment with adalimumab for rheumatoid arthritis**

Sirs,

The increasing use of tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) antagonists in the treatment of inflammatory rheumatic disorders, while driving a remarkable clinical improvement for many patients, has raised concerns on possible side effects. Among these, a few cases of rheumatoid nodules formation following treatment with etanercept have been signalled (1-3), approaching previous descriptions related to DMARDs therapy (4-7).

We report a case of a 45 year-old Caucasian woman affected by rheumatoid arthritis (RA) who developed rheumatoid nodules while taking adalimumab. The patient was diagnosed as having RA in 1997 and treated with several DMARDs in association with low-dose corticosteroids and nonsteroidal anti-inflammatory drugs. She was referred to our rheumatology division in September 2002: erosive polyarthritis involving wrists, hands and feet, positivity of rheumatoid factor, and increased values of ESR (58 mm/1<sup>st</sup> hr) and CRP (12 mg/L) were demonstrated. In March 2003, the patient was started on adalimumab 40 mg subcutaneously every other week, with add-on prednisone and oxaprozin obtaining prompt clinical and laboratory (ESR 36 mm/1<sup>st</sup> hr; CRP 0.5 mg/L) improvement. In October 2005, the patient experienced again a polyarticular flare and elevated ESR and CRP values. Moreover, she complained of the appearance of subcutaneous nodules in the extensor side of the elbows starting five months before. The ultrasonographic assessment, using a high resolution linear probe, showed changes suggestive of rheumatoid nodules, characterized by hypoechoic formations with a round shape and well defined margins permitting a good definition from the nearby tissues (Fig. 1). The dosing frequency of adalimumab was augmented to 40 mg subcutaneously every week. Two months later the size and number of the nodules remained unchanged, as confirmed by ultrasound assessment, while the articular involvement worsened (ESR 90 mm/1<sup>st</sup> hr; CRP 9 mg/L).

Rheumatoid nodules are considered as the most characteristic extra-articular histopathological lesion in RA, usually associated with a more severe disease (8). The pathogenetic mechanism is still unknown, but vasculitis is deemed as one of the most suitable, since endothelial cell injury, favoured by complement activation and immunoglobulin deposition, is an essential component of both early and long-standing nodules (9). The main infiltrating inflam-



**Fig. 1.** Posterior transverse ultrasound scan of the right elbow of the patient: the hypoechoic formation in the subcutaneous region is suggestive of a rheumatoid nodule.

matory cell inside the rheumatoid nodule is the macrophage, which is also the major cell producing TNF- $\alpha$  (8). Rheumatoid nodule formation has been described following treatment with etanercept, a recombinant TNF- $\alpha$  receptor fusion protein. Our case represents the first description of the appearance of such nodules after the introduction of adalimumab, an anti-TNF- $\alpha$  human monoclonal antibody. In the previous reports the emergence of nodules ranged from eight weeks to seventeen months after the commencement of etanercept (1-3), while our patient developed nodulosis after two years of adalimumab treatment. The new formation of nodules may be a benign side effect of treatment, resulting from increased cell death and enhanced chemotaxis of inflammatory cells by the enlarging necrotic centre of the rheumatoid nodule (2). Indeed, *in vitro* models have demonstrated that adalimumab is capable to lyse surface TNF-expressing cells in the presence of complement (10) and the activation of complement has been largely documented within the rheumatoid nodule. Otherwise, rheumatoid nodules may represent the expression of a chronic inflammation, less susceptible to TNF- $\alpha$  blockers (2), due to the lower TNF- $\alpha$  concentrations compared with the synovium (8). Undoubtedly our patient presented predisposing factors for the development of nodulosis, including a longstanding disease with severe articular involvement and rheumatoid factor positivity; yet, she did not exhibit the nodules until the treatment with adalimumab was introduced.

Surely further studies are needed to better define the relationship between TNF- $\alpha$  blockade and the appearance of these typical extra-articular manifestations of RA.

R. SCRIVO, MD, *Research Fellow*  
 A. SPADARO, MD, *Associate Professor*  
 A. IAGNOCCO, MD, *Assistant Professor*  
 G. VALESINI, MD, *Professor*

*Dipartimento di Clinica e Terapia Medica Applicata – Divisione di Reumatologia, Università di Roma “La Sapienza”, Azienda Policlinico Umberto I, Viale del Policlinico 155, 00161 Roma, Italy.*

*Please address correspondence and reprint requests to: Prof. Antonio Spadaro, Dipartimento di Clinica e Terapia Medica Applicata, Divisione di Reumatologia, Università di Roma “La Sapienza”, Azienda Policlinico Umberto I, Viale del Policlinico 155, 00161 Roma, Italy. E-mail: a.spadaro.reuma@virgilio.it*

**References**

1. KEKOW J, WELTE T, KELLNER U, PAP T: Development of rheumatoid nodules during anti-tumor necrosis factor therapy with etanercept. *Arthritis Rheum* 2002; 46: 843-4.
2. CUNNANE G, WARNOCK M, FYE KH, DAIKH DI: Accelerated nodulosis and vasculitis following etanercept therapy for rheumatoid arthritis. *Arthritis Care Res* 2002; 47: 445-9.
3. HÜBSCHER O, RE R, IOTTI R: Pulmonary rheumatoid nodules in an etanercept-treated patient. *Arthritis Rheum* 2003; 48: 2077-8.
4. JUN JB, KOH HK, BAE SC, YOO DH, KIM SY: Accelerated nodulosis immediately after initiating weekly low dose methotrexate for rheumatoid arthritis. *Clin Exp Rheumatol* 1999; 17: 127.
5. LANGEWITZ P, MAGUIRE L, UROWITZ M: Accelerated nodulosis during azathioprine therapy. *Arthritis Rheum* 1991; 34: 123-4.
6. SPADARO A, FIORE D, IAGNOCCO A *et al.*: Rheumatoid nodules and cyclosporin A treatment. *Int J Clin Pharmacol Res* 1994; 14: 75-8.
7. BRAUN MG, VAN RHEE R, BECKER-CAPELLER D: Development and/or increase in rheumatoid nodules in RA patients following leflunomide therapy. *Z Rheumatol* 2004; 63: 84-7.
8. WIKANINGRUM R, HIGHTON J, PARKER A *et al.*: Pathogenic mechanisms in the rheumatoid nodule. *Arthritis Rheum* 1998; 41: 1783-97.
9. KATO H, YAMAKAWA M, OGINO T: Complement mediated vascular endothelial injury in rheumatoid nodules: a histopathological and immunohistochemical study. *J Rheumatol* 2000; 27: 1839-47.
10. SALFELD J, KAYMAKALAN Z, TRACEY D *et al.*: Generation of fully human anti TNF-antibody D2E7 [Abstract]. *Arthritis Rheum* 1998; 41 (Suppl. 9): S57.