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### Sarcoid-like Granulomatous Disease Following Etanercept Treatment for Rheumatoid Arthritis

*To the Editor:*

Sarcoidosis is a multisystem disorder of unknown etiology with both pulmonary and extrapulmonary manifestations typically characterized by non-caseating granulomas or nodular granulomata<sup>1</sup>. We describe a case of sarcoid-like granulomatous disease with respiratory and parotid involvement developing in a patient with rheumatoid arthritis (RA) treated with etanercept.

A 52-year-old woman developed bilateral parotid gland swelling, lethargy, sicca symptoms, and abdominal pain following 18 months of etanercept treatment for a severe flare of RA. She had a history of seropositive erosive RA, treated with corticosteroids prior to the use of etanercept, and cutaneous lupus erythematosus. An initial clinical diagnosis of secondary Sjögren's syndrome was made and the etanercept was discontinued.

Histological examination of her parotid biopsy showed multiple granulomata with prominent central necrosis (Figure 1A). Stains for histoplasma, nocardia, and Ziehl-Neelsen stain for mycobacterium tuberculosis (TB) and non-tuberculous mycobacteria were negative. A Grocott stain of the parotid biopsy for fungi was also negative, as were bacterial and mycobacterial cultures. Polymerase chain reaction (PCR) for TB was negative. Her purified protein derivative test prior to treatment with etanercept was negative, she denied TB contacts and she had not received bacillus Calmette-Guérin vaccination.

She presented again 6 weeks later with shortness of breath, dry cough, and further abdominal pain. On examination she was noted to be tachypneic (respiratory rate 22/min) although the lungs were clear on auscultation; abdominal and cardiovascular examinations were unremarkable and there were no eye or cranial nerve abnormalities. Blood tests revealed lymphopenia  $0.4$  (normal  $1.0$ – $2.8$ )  $\times 10^9/l$  on full blood count; however, she had normal hemoglobin, liver and renal function, C-reactive protein, thyroid function, lactate dehydrogenase, normal corrected calcium and angiotensin-converting enzyme levels. The erythrocyte sedimentation rate

was 35 mm/h. Immunological tests showed a positive rheumatoid factor and an antinuclear antibody level of 3.8 IU (normal 0–0.9) with an anti-dsDNA titer of 1:180 (normal 0–50), but negative antibodies to extractable nuclear antigens. Immunoglobulin, antineutrophil cytoplasmic antibodies, and complement levels were normal.

Computerized tomography (CT) of the chest revealed symmetrical mediastinal lymphadenopathy with several small bronchopulmonary nodules (Figure 2). Transbronchial biopsy revealed noncaseating granulomata in the bronchial mucosa with large numbers of multinucleate giant cells and some surrounding lymphocytes typical of sarcoidosis (Figure 1B). CT of the abdomen was normal. Bronchoalveolar washings were negative for bacteria, mycobacterium, and fungi, as was PCR analysis for TB and atypical mycobacteria. Analysis of the type 1 cytokine profile indicated no defect in the interferon- $\gamma$  and interleukin 12 signaling pathways. She began taking prednisolone 40 mg daily, and this resulted in excellent symptomatic relief and radiological improvement.

Tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) has been implicated in the pathogenesis of granulomatous disease and TNF-blocking agents have been used successfully in their treatment; however, the efficacy of etanercept in these conditions remains controversial<sup>2</sup>. An open-label study of etanercept in 17 patients with pulmonary sarcoidosis was terminated early due to lack of effect<sup>3</sup>. In a randomized controlled trial (RCT) of 20 patients with methotrexate-refractory ocular sarcoidosis, no difference was observed in outcome between the active and placebo-treated groups<sup>4</sup>. Despite this, the results of a more recent multicenter RCT showed that infliximab therapy resulted in a statistically significant improvement in certain severe forms of chronic sarcoidosis<sup>5</sup>.

Our patient developed systemic sarcoid-like granulomatous disease during anti-TNF treatment. It was not possible to determine whether administration of etanercept itself or consequent reduction of corticosteroid treatment resulted in the development of the condition. The possibility of mycobacterial or nonmycobacterial infection (especially in view of the cavitating necrosis found in parotid glands) cannot be totally excluded, but routine stains, longterm culture, and PCR all failed to detect any pathogenic organism. In addition there was no evidence of mycobacterial disease on followup despite corticosteroid therapy.

Sarcoidosis is recognized to cause necrosis within granulomas in up to 40% of sarcoid tissue biopsies<sup>6</sup>. The significant improvement in her general condition and almost instant response of the parotid gland swelling and respiratory symptoms to steroid treatment again makes an infectious cause, including TB, highly unlikely.

Data are limited on the use of TNF antagonists in sarcoidosis, and it is apparent that the role of TNF is rather complex in the evolution of granulomatous process. TB remains one of the most frequent opportunistic infections reported in association with use of infliximab<sup>7</sup>. The pharmacokinetics, mode of TNF inhibition, and binding of lymphotoxin- $\alpha$  (etanercept only) may explain differences in therapeutic efficacy of different TNF inhibitors and the incidence of granuloma-dependent infections among them<sup>8</sup>. There are other reports describing the development of pulmonary non-necrotizing granulomatosis due to etanercept therapy and a rapid response to steroid treatment<sup>9,10</sup>. The phenomenon of a granulomatous response to etanercept requires further investigation to explain the underlying mechanism.

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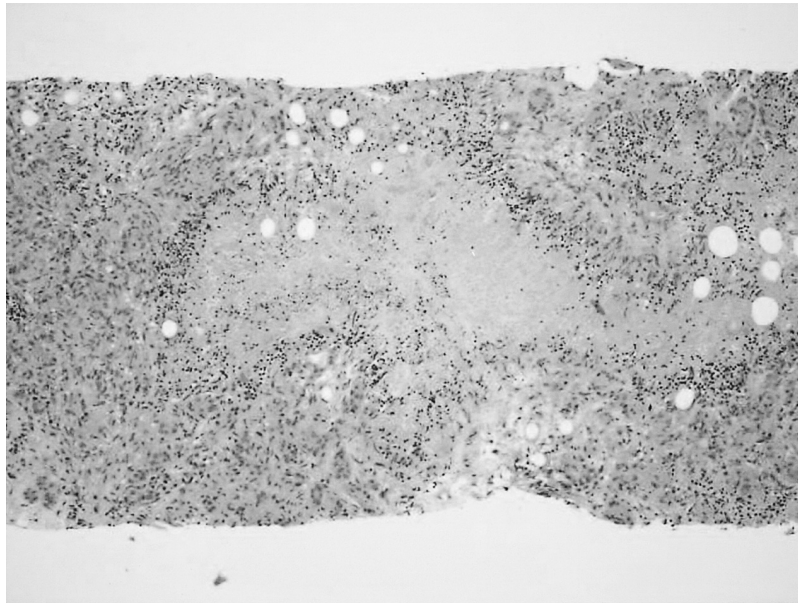


Figure 1A. Low power view of parotid biopsy showing granulomata with central necrosis and palisading histiocytes.

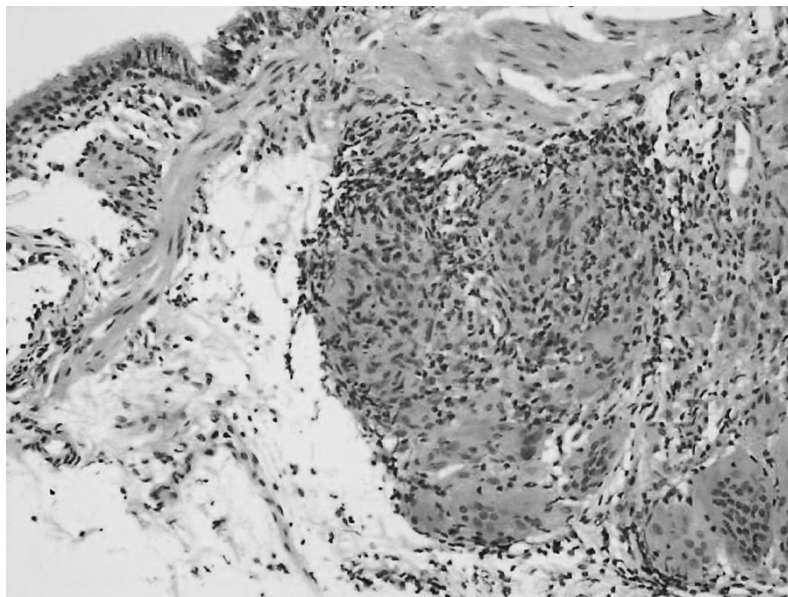


Figure 1B. High power view of bronchial mucosa showing noncaseating granuloma with giant cells.

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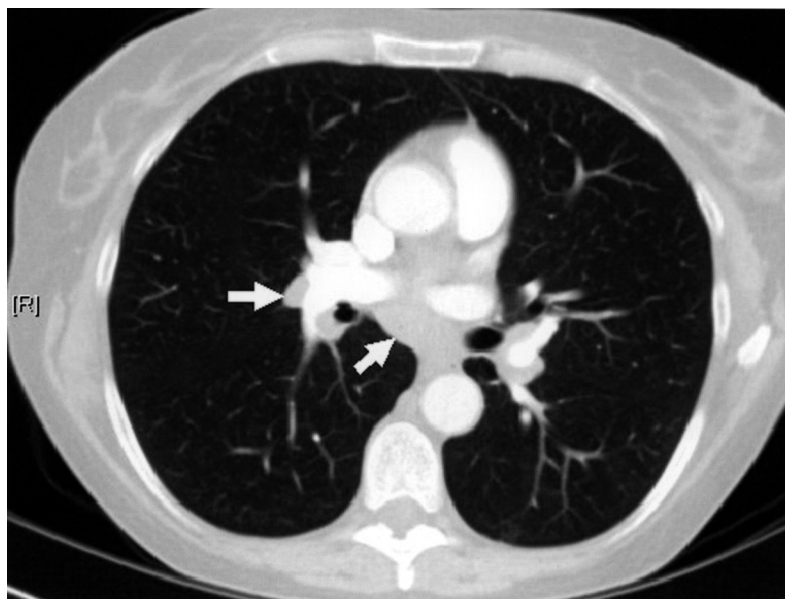


Figure 2. CT of the chest revealing mediastinal lymphadenopathy (arrows) and micronodules within the lung parenchyma.

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### C-Reactive Protein in Primary Antiphospholipid Syndrome

To the Editor:

In their article, Sailer, *et al*<sup>1</sup> did not find a relationship between the acute phase reactants C-reactive protein (CRP) and fibrinogen with thrombosis in patients with lupus anticoagulants (LAC). To add to this topic we measured CRP (immunoturbidimetry, Beckman, CV < 4%: linear range 0.04–84 mg/dl) in 20 consecutive patients with primary antiphospholipid syndrome (PAPS) (14 women, 6 men, ages  $41 \pm 15$  yrs, mean disease duration  $9.8 \pm 4.3$  yrs; myocardial infarction  $n = 2$ , ischemic stroke  $n = 6$ , deep vein thrombosis  $n = 12$ , smokers  $n = 6$ ) diagnosed according to established criteria<sup>2</sup>; in 24 patients with inherited thrombophilia (IT) (16 women, 8 men, ages  $55 \pm 17$  yrs, mean disease duration  $8.6 \pm 4.4$  yrs; myocardial infarction  $n = 2$ , ischemic stroke  $n = 4$ , deep vein thrombosis  $n = 18$ , factor V Leiden heterozygous  $n = 16$ , protein C deficiency  $n = 4$ , protein S deficiency  $n = 4$ , smokers  $n = 4$ ); and in 30 healthy subjects (15 blood donors, 15 medical personnel, 20 women, 10 men, mean age  $48 \pm 15$  years, smokers  $n = 8$ ). Occlusive events had been diagnosed by Doppler ultrasound, angio computerized tomography, angio magnetic resonance imaging, and electrocardiogram as indicated. All patients with PAPS and 22 with IT were taking warfarin at the time of CRP measurement, whereas the remaining patients with IT were taking aspirin (75 mg/day). All participants gave informed consent to the study, none self-reported an infection in the previous 4 weeks, and urinary dipstick test for nitrates was negative in all. In the PAPS group, IgG and IgM anticardiolipin antibodies (aCL; enzyme immunoassay, Cambridge Life Sciences, UK) had been detected twice 6

weeks apart at the time of diagnosis and then yearly thereafter. All patients with PAPS had a LAC measurement at diagnosis. Those detected as activated partial thromboplastin time ( $n = 16$ ) were reconfirmed ( $n = 16$ ) by comparing a sensitive and an insensitive reagent to the LAC<sup>3</sup>. In the PAPS group, median IgG aCL was 102 GPL (range 11–479 GPL) and median IgM aCL was 10 MPL (range 2–847 MPL). The PAPS group displayed higher mean CRP than the IT and control groups (Figure 1). Within the PAPS group, higher CRP was noted in patients with arterial rather than venous events ( $\text{CRP } 4.8 \pm 3.2$  vs  $1.9 \pm 1.5$ ;  $p = 0.02$ , Mann-Whitney t-test) and in patients with multiple ( $n = 8$ ) rather than single events ( $n = 12$ ) ( $4.9 \pm 3.3$  vs  $1.8 \pm 1.2$  mg/dl;  $p = 0.02$ , Mann-Whitney t-test), and a similar pattern was noted in the IT group ( $3.7 \pm 3.1$  vs  $1.3 \pm 0.7$  mg/dl; nonsignificant). Moreover, IgG aCL correlated to CRP titer (Figure 2A) and to plasma fibrinogen (Clauss assay; Figure 2B). Having employed an IT control group rather than a LAC-positive thrombosis-negative group, we came to the same conclusion reached by Sailer, *et al*<sup>1</sup>, that of a possible low-grade inflammatory state in PAPS. However, the involvement of CRP in the type and number of occlusive events is being investigated further, as it might represent a

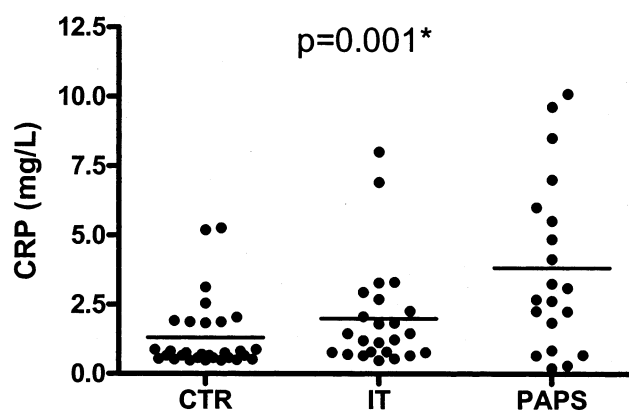


Figure 1. Mean CRP in healthy controls (CTR), and patients with inherited thrombophilia (IT) and primary antiphospholipid syndrome (PAPS). \*Kruskal-Wallis analysis of variance.

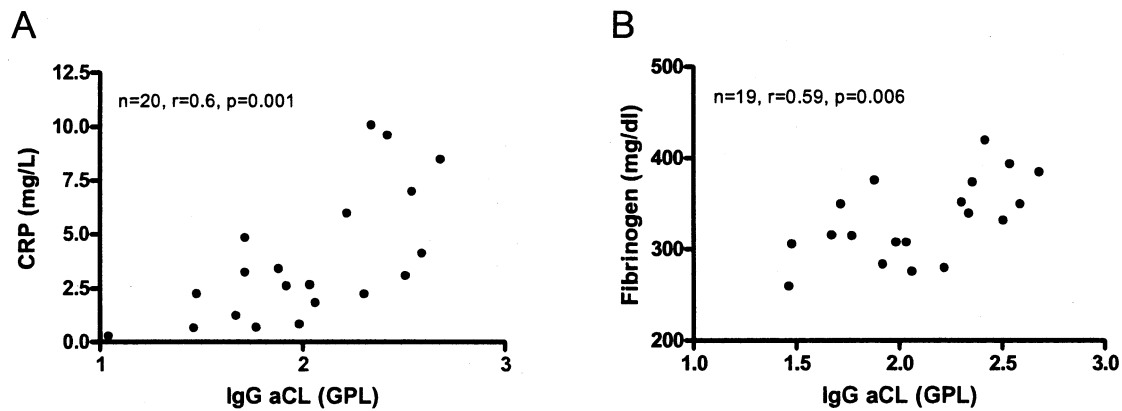


Figure 2. Pearson's correlation between log-transformed IgG aCL and CRP (A) and fibrinogen (B).

worthwhile and inexpensive test to predict persistence of antiphospholipid antibodies<sup>4</sup> and severity of antiphospholipid related vascular damage<sup>5</sup>.

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