

## Abrupt Development of Sarcoidosis with a Prodromal Increase in Plasma Osteopontin in a Patient with Rheumatoid Arthritis During Treatment with Etanercept

To the Editor:

Biologic disease-modifying antirheumatic drugs (DMARD) targeting tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) are very efficacious and the number of patients with rheumatoid arthritis (RA) treated with these drugs is increasing rapidly. Because granulomatous diseases as typified by sarcoidosis are considered to develop in the Th1 cytokine milieu dominated by interferon- $\gamma$  (IFN- $\gamma$ ) and TNF- $\alpha$ , anti-TNF- $\alpha$  agents have been used for treatment of sarcoidosis. Reports show that infliximab is effective, while etanercept is not, in the treatment of sarcoidosis<sup>1,2</sup>. In contrast, anti-TNF- $\alpha$  agents may have induced sarcoidosis in patients with RA and spondyloarthritis<sup>3-6</sup>.

The patient we describe had acute onset of sarcoidosis in several organs simultaneously after a long period of remission of RA while receiving etanercept. Based on serum and plasma levels of laboratory indicators related to sarcoidosis, the condition might have developed as quickly as within 1 or 2 months.

A 52-year-old Japanese woman was diagnosed with RA in 1980 and had been treated with several DMARD such as injectable gold salt, sulfasalazine, actarit, methotrexate, and mizoribine with no appreciable effects. Leflunomide was started in 2000 and etanercept 25 mg/week was added in January 2007, increased to 50 mg/week in July 2007. The RA became quiescent under etanercept treatment and the Disease Activity Score 28 fell to 2.22 from 4.17. She had been in clinical remission until a fever of 38.5°C and general malaise developed suddenly in March 2008, when she was admitted to hospital.

Evaluation showed fine crackles in both lung fields; they were due to rheumatoid lung and no change was observed in intensity. Superficial lymph nodes were not palpable. Swelling and tenderness were not detected in any joint. Pitting edema was detected bilaterally in the pretibial and pedal regions. The skin on both thighs became pruritic, although no eruption

was observed on her body. Laboratory data showed the following: white blood cells 6300/ $\mu$ l; hemoglobin 11.4 g/dl; platelets 32.3  $\times$  10<sup>4</sup>/ $\mu$ l; C-reactive protein 10.93 mg/dl; AST 53 mU/ml (normal < 30); ALT 46 mU/ml (< 30); ALP 983 mU/ml (< 330); blood urea nitrogen 16 mg/dl; and creatinine 0.40 mg/dl.

Lymph node enlargement in the pulmonary hilar regions and mediastinum was seen on plain chest radiograph and confirmed by computed tomography scan. Sputum culture and polymerase chain reaction investigation were negative for acid-fast bacilli including *Mycobacterium tuberculosis*. A purified protein derivative skin test was negative. Gallium scintigraphy showed abnormal uptake in the salivary glands, paratracheal region, and right quadriceps muscle (Figure 1A). Fat-saturated T1-enhanced magnetic resonance imaging (MRI) also showed high intensity at the right quadriceps muscle (Figure 1B). Although a skin eruption was not observed, her pruritus became more severe.

Sarcoidosis was one of the differential diagnoses considered, and related data were collected: angiotensin converting enzyme (ACE) 31.5 mU/ml (normal < 21.4); lysozyme 27.2  $\mu$ g/ml (< 10.2); soluble interleukin 2 receptor (IL-2R) 4830 U/ml (< 466); IFN- $\gamma$  0.9 IU/ml (< 0.1); and osteopontin 327 ng/ml (normal range not determined).

Biopsy specimens were obtained from the liver and skin from the most pruritic area, and both histologies showed noncaseating granulomata with giant cells and lymphocyte infiltration (Figure 1C). The diagnosis of sarcoidosis was based on these histologic findings along with laboratory data. Prednisone 30 mg/day led to rapid symptomatic improvement.

The patient developed sarcoidosis 14 months after the initiation of etanercept for treatment of RA. There are 19 case reports of sarcoidosis developing during anti-TNF therapy (including this one): 10 cases on etanercept, 6 on infliximab, and 3 on adalimumab. At first, the occurrence of sarcoidosis was reported mainly in patients taking etanercept; however, there are an increasing number of cases of sarcoidosis during anti-TNF therapy other than etanercept.

Sarcoidosis is usually diagnosed incidentally based on radiographic

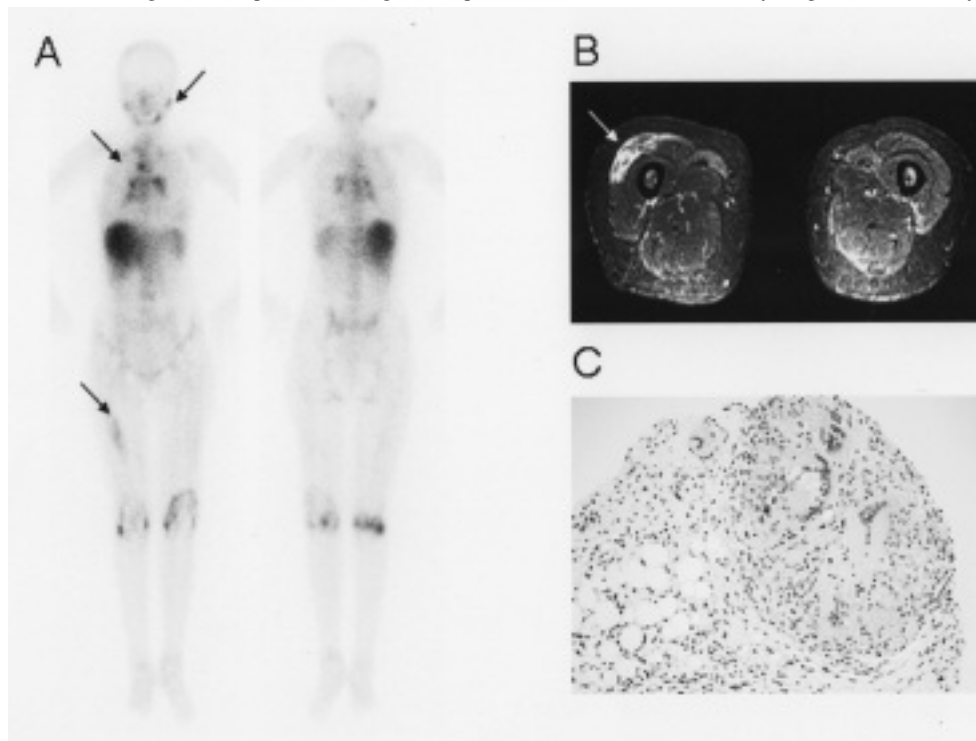


Figure 1. A. Gallium scintigraphy showed abnormal uptake in the salivary glands (upper arrow), hilar and paratracheal lymph nodes (middle arrow), and the right quadriceps muscle (lower arrow). B. Fat-saturated T1-enhanced MRI showed high intensity at the right quadriceps muscle (arrow). C. Biopsy specimen from the skin showed a non-caseating granuloma with multinucleated giant cells.

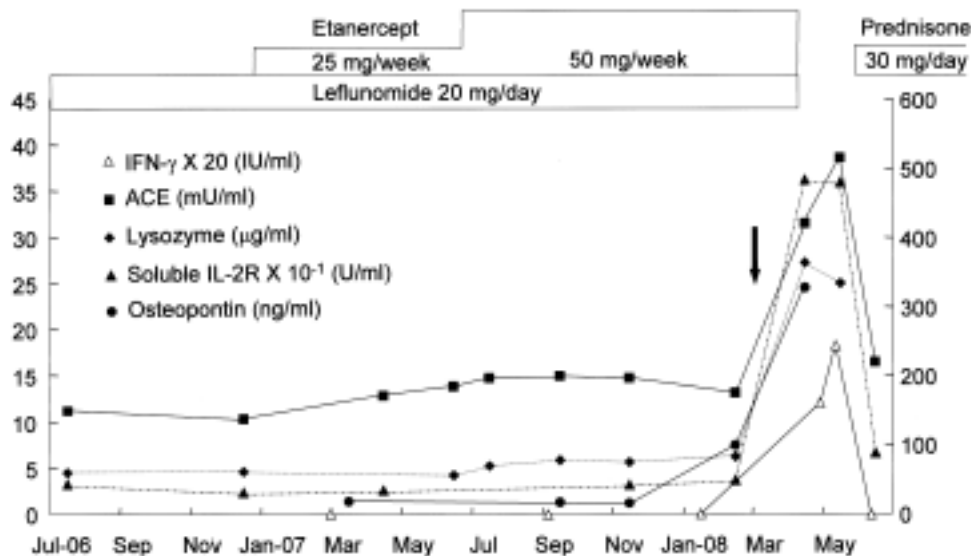


Figure 2. The clinical course of this patient. Arrow indicates date of development of fever and general malaise. Left y-axis shows concentrations of IFN- $\gamma$ , ACE, and lysozyme; right y-axis shows soluble IL-1R and osteopontin. ACE: angiotensin-converting enzyme; IL-2R: interleukin 2 receptor; IFN- $\gamma$ : interferon- $\gamma$ .

findings and the clinical course is usually indolent, although there are cases with more severe clinical manifestations. Our case showed an acute onset with diffuse organ distribution: salivary glands, muscle, liver, skin, and lung. There were no symptoms, including joint pain, when she presented at the end of February 2008; she was still receiving etanercept along with leflunomide. However, fever and general malaise necessitating hospitalization developed at the end of March. We measured, retrospectively and longitudinally, the serum or plasma levels of ACE, lysozyme, soluble IL-2R, osteopontin, and IFN- $\gamma$ , and found that they all increased steeply at the time of admission compared to the previous hospital visits (Figure 2). Longitudinal and repeated measurements of these variables have not previously been reported in patients with sarcoidosis, and accumulation of such data might give us a clue to the pathogenesis of sarcoidosis in the setting of TNF blockade or sarcoidosis in general.

Osteopontin is a noncollagenous matrix protein produced by macrophages and T lymphocytes that is very important for Th1 response<sup>7</sup>. A slight increase in plasma osteopontin level just before steep increases in other variables might deserve attention; osteopontin may portend the development of sarcoidosis and therefore could be important in pathogenicity<sup>8</sup>.

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