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# Sarcoidosis during etanercept treatment for rheumatoid arthritis in women with a history of bilateral oophorectomy

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**Abstract.** The therapeutic effects of anti-tumor necrosis factor (TNF) treatment are generally expected in sarcoidosis and in immune-mediated inflammatory diseases, such as rheumatoid arthritis (RA). Paradoxically, this treatment induces sarcoidosis in a small population of RA patients as a class effect. A safer anti-TNF therapeutic strategy requires understanding of the risk factors for sarcoidosis. In Japan, TNF inhibitor was introduced in 2003. We reviewed 226 consecutive patients (65 men and 161 women) who were newly diagnosed with sarcoidosis between 2003 and 2012 at Jichi Medical University Hospital, Japan. We detected 3 cases in which sarcoidosis developed during etanercept treatment for RA. All 3 cases were women who had undergone bilateral oophorectomy more than 20 years earlier. Taken together with our previous epidemiologic findings of a consistently maintained second peak after menopause in the age-specific distribution of sarcoidosis in women over four decades, long-term insidious ovarian dysfunction was a possible risk factor for sarcoidosis under certain conditions, especially during etanercept treatment. *(Sarcoidosis Vasc Diffuse Lung Dis 2016; 33: 178-181)*

**Key words:** sarcoidosis, anti-TNF treatment, ovarian dysfunction, regulatory T cells

**Abbreviations list:**

TNF = tumor necrosis factor;
IMIDs = immune-mediated inflammatory diseases;
RA = rheumatoid arthritis;
Th1 = T helper 1 cell;
ACE = angiotensin-converting enzyme;
IL = interleukin;
Treg = regulatory T cell

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## Introduction

Tumor necrosis factor (TNF)-α plays a key role in the pathophysiology of sarcoidosis and immune-mediated inflammatory diseases (IMIDs), such as rheumatoid arthritis (RA) (1, 2), and is considered a major therapeutic target. Recent genetic studies have demonstrated that the immunologic etiology of the disequilibrium between T helper 1 (Th1) and Th17 response and regulatory mechanisms was common to both disorders (3, 4). Anti-TNF treatment is expected to suppress the enhanced pathogenic effector T cell response and relieve disease activity in target tissues. Paradoxically, anti-TNF treatment triggered sarcoidosis in a small number of RA patients. The coexistence of RA with sarcoidosis is known to be

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very rare (5). However, after the introduction of TNF inhibitors in 2002, case reports on the development of sarcoidosis during RA treatment, especially that associated with etanercept (a soluble TNF receptor fusion protein), have accumulated.

In Japan, TNF inhibitor was introduced in 2003. We reviewed 226 consecutive patients (65 men and 161 women) who were newly diagnosed with sarcoidosis between 2003 and 2012 at Jichi Medical University Hospital, Japan. All patients who were admitted to or underwent bronchoscopy at our respiratory center were included in our previous epidemiological study (6). We detected three sarcoidosis cases that developed during etanercept treatment for RA, all of whom were women who had undergone bilateral oophorectomy more than 20 years earlier.

## Case Report

*Case 1*

A 63-year-old woman was referred to our Division of Pulmonary Medicine in February 2011 for bilateral hilar lymphadenopathy that was detected on physical examination. She had undergone bilateral partial oophorectomy for bilateral ovarian cyst rupture 20 years earlier. RA had been diagnosed in 1995 and she had been started on prednisone 2 mg per day. Etanercept treatment and methotrexate were added in 2005. Three years before her first visit to our department, she noticed four subcutaneous nodules in her right lower thigh; 3 months before, ophthalmology analysis revealed iritis and glaucoma. On the first visit, her serum levels of angiotensin-converting enzyme (ACE) and soluble interleukin (IL)-2 receptor were elevated at 25.1 mU/ml (normal, <21.4 mU/ml) and 1690 U/ml (normal, <466 U/ml), respectively. Gallium scintigraphy revealed lambda sign and abnormal uptake in both lacrimal glands. The tuberculin skin test was negative. Biopsy of the subcutaneous nodules that developed in her forearm revealed non-caseating epithelioid granulomas. Based on these findings, she was given a diagnosis of sarcoidosis.

*Case 2*

A 73-year-old woman was transferred to our Division of Nephrology in May 2012 because of impaired consciousness due to hypercalcemia, with a serum calcium level corrected to albumin of 14.4 mg/dl, after undergoing surgery for perforated duodenal ulcer. She had undergone total hysterectomy and bilateral oophorectomy for uterine cancer and myoma 22 years earlier. RA was diagnosed in 1996 and she was started on prednisone 10 mg per day. The prednisone dose was increased transiently to 30 mg per day because she developed anti-neutrophil cytoplasmic antibody-associated nephritis during levothyroxine treatment for chronic thyroiditis in 2000; it was later decreased to 2 mg per day. Although etanercept was added for RA resistant to initial treatment in January 2011, it was withdrawn at the time of duodenal perforation. Elevation of her serum calcium level was accompanied by elevation of serum levels of ACE, lysozymes, and soluble IL-2 receptor at 30.7 mU/ml, 30.4 μg/ml, and 2920 U/ml, respectively. Hyperglobulinemia was also detected. Computed tomography revealed mediastinal lymph node enlargement. The tuberculin skin test was negative. Based on these findings, the clinical diagnosis was sarcoidosis; her relatively high serum level of $1.25(OH)_2VitD_3$ was consistent with sarcoid granuloma formation. Increasing the dose of prednisone to 20 mg per day resolved the sarcoidosis, reduced the size of the mediastinal lymph nodes, and significantly decreased the serum levels of calcium, ACE, and lysozymes.

*Case 3*

A 70-year-old woman was referred and admitted to our Division of Gastroenterology for a liver biopsy in June 2010. During examination for sigmoid colon cancer, she had liver dysfunction and elevated serum levels of aspartate aminotransferase and alanine aminotransferase at 202 and 296 mU/ml, respectively. She had undergone total hysterectomy and bilateral oophorectomy for uterine myoma 30 years earlier. RA was diagnosed in 1989 and methotrexate with sodium aurothiomalate was started. In January 2006, infliximab was substituted for sodium aurothiomalate because of persistent arthralgia; however, it was withdrawn soon after because of the appearance of cutaneous pruritus. In November 2006, etanercept was added to methotrexate and was used until liver dysfunction was detected. Liver biopsy revealed scattered non-caseating epithelioid granulomas in the hepatic lobule, as well as findings of interface hepati-

tis, characteristic of autoimmune hepatitis. Both direct staining and polymerase chain reaction methods for acid-fast bacilli of liver specimens were negative. No acid-fast bacilli were detected in sputum, bronchoalveolar lavage fluid, gastric juice, or bone marrow specimens by smear, culture, or polymerase chain reaction. No fungi were detected in any specimens. The QuantiFERON-TB test was negative. Abdominal ultrasonography revealed lymphadenopathy around the hepatic artery. Hypercalcemia and hyperglobulinemia were also detected. A diagnosis of sarcoidosis complicated by autoimmune hepatitis was made and prednisone 40 mg per day was started.

## Discussion

Anti-TNF treatment is expected to suppress the enhanced pathogenic effector T cell response in target tissues and to relieve the disease activity of both sarcoidosis and RA. The pathogenesis of the paradoxic induction of sarcoidosis during anti-TNF treatment in a small number of RA patients is still unclear. However, the delicate immune balance of effector T cell response and regulatory mechanisms seemed to be crucial for the outcome of anti-TNF treatment (7). In the context of RA, one of the ways in which TNF-inhibitors relieve disease activity is by preventing pathogenic Th1 and Th17 cells from migrating into the affected joints. However, independent of their anti-inflammatory effect, TNF-inhibitors were reported to undesirably increase the number of pathogenic T cells by upregulating IL-12/23 p40 in the lymph nodes (8, 9). Monoclonal anti-TNFα antibodies, like infliximab, restore the regulatory T cell (Treg) suppressive function by targeting Tregs directly via the TNF receptor 2 and induce a new Treg population (10-12). The minimal influence of etanercept on Tregs seemed to partly explain why sarcoidosis induction is relatively common during treatment with etanercept. A safer anti-TNF therapeutic strategy requires understanding of the risk factors for sarcoidosis.

Here, we provided a clinical basis for the notion that prolonged deprivation of ovarian hormones may be a risk factor for sarcoidosis under certain conditions, especially during etanercept treatment. In Japan, there were at least 8 cases of sarcoidosis that occurred in RA patients under anti-TNF treatment; all were associated with etanercept use in women >45 years old (Table 1) (13-17). At our hospital, three consecutive patients with a similar pattern of sarcoidosis development were included in this study; all were women with a history of bilateral oophorectomy more than 20 years earlier. In Japan, as well as in Europe, the distribution of age at diagnosis is biphasic in women. Although our previous epidemiologic study in Japan showed a recent decline in the first peak that was modified by external environmental factors, the second peak in women aged ≥45 years was presumably accelerated by endogenous changes after menopause and has been consistently maintained over the last four decades (6).

Given the early clinical observations that women with previous diagnoses of sarcoidosis experienced remission during pregnancy and relapsed postpartum, we deduce that certain female reproductive and hormonal factors may reduce disease activity. In 2012, the

**Table 1.** Reported cases of sarcoidosis in rheumatoid arthritis patients under anti-TNF treatment in Japan

| References | Age, Sex | RA onset | Gynecology history | Drug/Months | Affected sites |
|---|---|---|---|---|---|
| 13) | 65F | 6 years earlier | * | Etanercept/25 | Lung, BHL, skin |
| 14) | 81F | 19 years earlier | * | Etanercept/42 | BHL, kidney |
| 15) | 65F | 2 years earlier | * | Etanercept/8 | Lung, BHL, heart |
| 16) | 68F | 10 years earlier | * | Etanercept/15 | Lung, BHL, meninges, periurethral |
| 17) | 75F | 7 years earlier | * | Etanercept/76 | Lung, skin, heart |
| Our Case 1 | 63F | 16 years earlier | Bilateral partial oophorectomy (20 years earlier), menopause (13 years earlier) | Etanercept/72 | BHL, eye, skin |
| Our Case 2 | 73F | 16 years earlier | Bilateral oophorectomy (22 years earlier) | Etanercept/13 | BHL |
| Our Case 3 | 70F | 21 years earlier | Bilateral oophorectomy (30 years earlier) | Etanercept/41 | Lung, liver |

RA: rheumatoid arthritis, F: female, BHL: bilateral hilar lymphadenopathy, *: unknown

first epidemiologic study to suggest protective roles of endogenous female hormones against sarcoidosis onset was reported (18). Moreover, this protective role of ovarian hormones against Th1 granulomatous formation has been supported by experimental studies. A sudden decline in circulating ovarian hormones after bilateral ovariectomy (19, 20) showed enhanced granulomatous reactions by forming local Th1 cytokine environments, followed by T cell migration. Increased expression of the transcription factor, T-bet, following loss of the immunomodulatory effects of ovarian hormones was reported to provoke local Th1 cytokine environments (19), which could increase susceptibility to granulomatous reactions in sarcoidosis (21). Apart from disease-specific phenomena, prolonged low levels of ovarian hormones during menopause were also shown to systematically promote differentiation of Th1 cells and to markedly decrease the size of Treg cell population (22).

However, given the small number of patients diagnosed with sarcoidosis during etanercept treatment for RA worldwide (N = 45 cases, including 7 men and 5 women, <45 years old) (23), the proposed female endogenous risk factor is still speculative. Such sex and age distribution may be accounted for not only by the TNF inhibitors and the rheumatic diseases for which they are used, but also by race. In addition, the possibility that this distribution reflects the risk factor for the rheumatic disease itself cannot be ruled out. Indeed, women were more likely than men to acquire sarcoidosis and there were several pre-menopausal women who developed the disease. Further studies are needed to understand the pathogenesis and risk factors of paradoxical sarcoidosis induction during anti-TNF treatment and this may give additional insights into the immunologic etiology of sarcoidosis.

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