

[CASE REPORT]

Development of *Propionibacterium acnes*-associated Sarcoidosis During Etanercept Therapy

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Abstract:

Although numerous recent studies have reported the development of sarcoidosis in patients treated with tumor necrosis factor alpha (TNF- α) inhibitors, it is unclear whether the pathogenesis of drug-induced sarcoidosis is identical to that of spontaneous sarcoidosis. We herein present the case of a patient who developed sarcoidosis 6 months after the introduction of etanercept as treatment for rheumatoid arthritis. Typical clinical symptoms with noncaseating epithelioid granulomas detected in a mediastinal lymph node specimen were consistent with the diagnosis of sarcoidosis. Immunohistochemistry revealed *Propionibacterium acnes* in the noncaseating granulomas. The present findings suggest that *Propionibacterium acnes* is a cause of sarcoidosis, even when the disease is induced by TNF- α inhibitors.

Key words: sarcoidosis, etanercept, TNF- α , *Propionibacterium acnes*

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Introduction

Sarcoidosis is a systemic inflammatory disorder characterized by noncaseating granuloma and commonly manifests in the lungs, eyes, skin, and heart (1). Previous reports indicate that tumor necrosis factor alpha (TNF- α) is critical in the formation of granulomas and is therefore a potential therapeutic target for the treatment of granulomatous diseases. However, some patients with chronic inflammatory disorders such as rheumatoid arthritis (RA) unexpectedly develop sarcoidosis after treatment with TNF- α inhibitors (2, 3). Numerous recent studies have reported cases of sarcoidosis associated with drugs such as TNF- α inhibitors and immune checkpoint inhibitors (4, 5). These cases have been referred to by some researchers as drug-induced sarcoidosis-like reactions (DISRs) (6). Chopra et al. reported that the clinical manifestations of sarcoidosis and DISRs are similar; however, unlike sarcoidosis, DISRs often resolve when the offending drug is discontinued and recur with re-challenge (6). Although the clinical characteristics of these conditions differ to some extent, it is unclear whether the pathogenesises of

DISRs and sarcoidosis are distinct.

Propionibacterium acnes (*P. acnes*) has been extensively studied as a causative microorganism in sarcoidosis (7-11). Interestingly, Negi et al. reported that immunohistochemistry using a specific monoclonal antibody of *P. acnes* can discriminate sarcoid and non-sarcoid granulomas, including the sarcoid reaction of malignant tumors (11).

We herein report a case in which sarcoidosis developed during etanercept treatment. Immunohistochemistry revealed *P. acnes* in the patient's noncaseating granulomas.

Case Report

A 54-year-old woman was admitted to another hospital in August X for pain in multiple joints. RA was diagnosed and etanercept treatment was started. Congestion of the bulbar conjunctiva developed 6 months after the start of etanercept treatment, and iritis was diagnosed by an ophthalmologist. Bilateral hilar lymphadenopathy was noted in a health exam in December X+1, after which she was referred to our institution for further examination.

A physical examination revealed mild congestion in both

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Table 1. Laboratory Data on Admission.

Blood chemistry		Immunological variables	
Total protein	7.2 g/dL	T-SPOT. TB	Negative
Albumin	3.6 g/dL	Anti-MAC antibody	Negative
Aspartate aminotransferase	30 U/L	Angiotensin-converting enzyme	28.0 U/L
Lactate dehydrogenase	217 U/L	Soluble IL-2 receptor	1,630 U/mL
Urea nitrogen	14 mg/dL	Tumor necrosis factor- α	3 pg/mL
Creatinine	0.6 mg/dL	Arterial blood gas analysis	
Calcium	8.7 mg/dL	pH	7.41
Phosphorus	4.1 mg/dL	PaCO ₂	39.3 mm Hg
C-reactive protein	11.1 mg/dL	PaO ₂	99.5 mm Hg
Krebs von den Lungen-6	269 U/mL		
Brain natriuretic peptide	30.4 pg/mL		
Procalcitonin	0.09 ng/mL		
Complete blood count			
White blood cell count	5,300 / μ L		
Red blood cell count	446 \times 10 ⁴ / μ L		
Hemoglobin	13.3 g/dL		
Platelet count	26.7 \times 10 ⁴ / μ L		

PaCO₂: partial pressure of arterial carbon dioxide, PaO₂: partial pressure of arterial oxygen

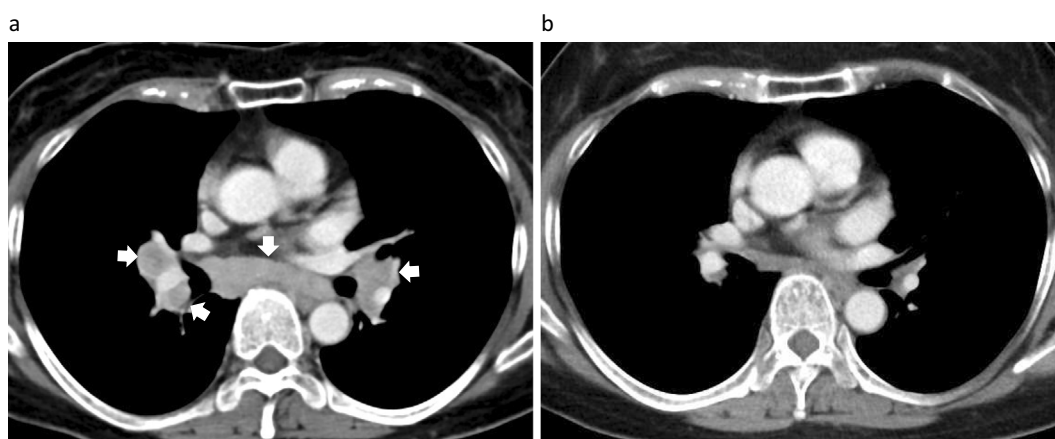


Figure 1. Chest computed tomography (CT) images. (a) A chest contrast-enhanced CT image obtained on admission. The white arrows indicate mediastinal and hilar lymphadenopathy. (b) At 1 year after the discontinuation of etanercept, the size of the lymph nodes had decreased.

eyes but no fever, skin lesions, or abnormal sounds on chest auscultation. A purified protein derivative skin test yielded a negative result. The laboratory findings are summarized in Table 1. The angiotensin-converting enzyme (ACE) and soluble interleukin-2 receptor (sIL-2R) levels were elevated. Pulmonary function testing revealed a normal respiratory function, and the arterial partial pressure of oxygen (PaO₂) was 99.5 mmHg in a blood gas analysis. No abnormal findings were observed on electrocardiography or echocardiography.

A chest radiograph showed bilateral hilar lymphadenopathy, and a contrast-enhanced chest computed tomography (CT) image showed mediastinal and hilar lymphadenopathy (Fig. 1a) without abnormal shadows in the lung fields. Positron emission tomography showed significant increases in the fluoro-2-deoxy-D-glucose uptake in the mediastinal and

hilar lymph nodes. Bronchoscopy was performed to confirm the diagnosis. A bronchoalveolar lavage fluid analysis showed an elevated CD4/8 ratio (6.73) and high lymphocyte fraction (macrophages, 63%; lymphocytes, 31%; neutrophils, 5%; and eosinophils, 1%). A tissue specimen was obtained from a mediastinal lymph node (#7) by endobronchial ultrasonography-guided transbronchial needle aspiration (EBUS-TBNA), and a histopathologic analysis showed formation of a loose noncaseating epithelioid granulomas (Fig. 2a), without evidence of mycobacterium tuberculosis infection, as indicated by Ziehl-Neelsen staining. Immunohistochemistry using a specific monoclonal antibody against *P. acnes* lipoteichoic acid (PAB antibody) (11) revealed *P. acnes* in several granulomas in the tissue (Fig. 2b). These findings indicated a diagnosis of sarcoidosis, and etanercept treatment was implicated as the cause of the disease.

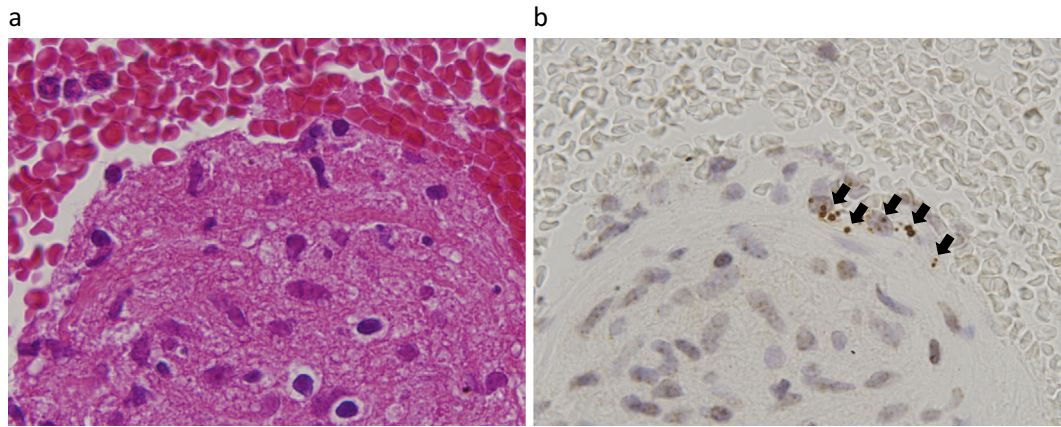


Figure 2. Endobronchial ultrasound-guided transbronchial needle aspiration was used to collect a lymph node specimen. (a) Hematoxylin and Eosin staining shows a noncaseating epithelioid cell granuloma. (b) Immunohistochemical staining with a specific monoclonal antibody against *Propionibacterium acnes* lipoteichoic acid (PAB antibody) shows positive reaction products (black arrows) in the granuloma.

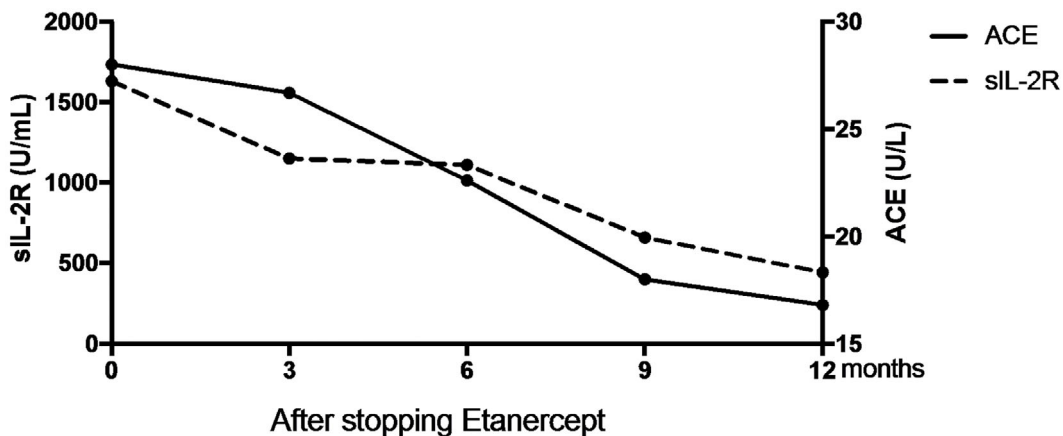


Figure 3. Changes in the serum biomarkers of sarcoidosis after discontinuation of etanercept. The angiotensin-converting enzyme (ACE) and soluble IL-2 receptor (sIL-2R) levels decreased after the cessation of etanercept discontinued.

Etanercept treatment was stopped and a follow-up examination was performed. The serum levels of ACE and sIL-2R gradually decreased without treatment after the discontinuation of etanercept (Fig. 3). A chest CT image showed that the mediastinal and hilar lymph nodes were smaller after 1 year (Fig. 1b), which indicated improvement without therapeutic intervention.

Discussion

Sarcoidosis is diagnosed based on compatible clinical features, radiological findings, and histological evidence of noncaseating epithelioid granulomas (1). Our patient developed iritis followed by bilateral hilar lymphadenopathy. In addition, biomarkers, including ACE and sIL-2R, were markedly elevated at the disease onset, which are findings consistent with sarcoidosis. EBUS-TBNA confirmed the presence of noncaseating epithelioid cell granulomas in the

mediastinal lymph nodes. The patient developed sarcoidosis during etanercept treatment and improved without therapeutic intervention after the cessation of etanercept. Thus, the final diagnosis was sarcoidosis induced by etanercept.

Previous studies found that TNF- α was important in granuloma formation in animal models of helminth infection (12-14) and in humans (15, 16). TNF- α is a key cytokine in the pathogenesis of sarcoidosis and a potential target of sarcoidosis treatment. In fact, based on small clinical trials, it has been reported that TNF- α inhibitors other than etanercept might be effective for sarcoidosis treatment (17-19). Interestingly, numerous recent studies have reported the development of sarcoidosis after TNF- α inhibitor treatment for systemic diseases. A literature search identified 63 cases of sarcoidosis due to TNF- α blocker treatment (Table 2). Most cases were caused by etanercept (68%), as occurred in our patient. Infliximab and adalimumab are monoclonal antibodies that recognize monomeric and trimeric sol-

Table 2. Summary of Reported Cases of Sarcoidosis Development after Treatment with a TNF- α Inhibitor.

	No. of patients	TNF- α inhibitor E/I/A	Time to onset (months)	Underlying disease	Treatment
Reported cases	63	43/12/8	24 \pm 22	RA 36, AS 11, PsA 10, JIA 4, SAPHO 1, Crohn 1	Discontinuation 31 Corticosteroids 28 Not available 4
Present case	1	Etanercept	8	RA	Discontinuation

E: etanercept, I: infliximab, A: adalimumab, RA: rheumatoid arthritis, AS: ankylosing spondylitis, PsA: psoriatic arthritis, JIA: juvenile idiopathic arthritis, SAPHO: Sapho syndrome, Crohn: Crohn disease

uble TNF and transmembrane TNF. In contrast, etanercept is the extracellular domain of the TNF receptor that is linked to the Fc and which only recognizes soluble trimeric TNF. Although the higher incidence of sarcoidosis due to etanercept treatment may be attributable to these different mechanisms of TNF- α inhibition, the pathogenesis of this condition has not been thoroughly studied.

Sarcoidosis is also induced by immune checkpoint inhibitors. Several recent studies reported that sarcoidosis or sarcoid-like granulomatosis developed in patients with malignant tumors treated by monoclonal antibodies against cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) and programmed death 1 (PD-1) (4, 5). Braun et al. reported that the PD-1 pathway in CD4 T cells was upregulated in sarcoidosis (20). PD-1 is a marker of lymphocyte exhaustion; thus, chronic lymphocytic inflammation may be associated with the pathogenesis of sarcoidosis. Enhanced lymphocyte proliferation by blockade of co-inhibitory signalling by immune checkpoint inhibitors is thought to be related to disease development.

Sarcoidosis is believed to be caused by an immune response after exposure to environmental factors, including infectious agents, in genetically susceptible individuals. Accumulating evidence suggests that *P. acnes* is the causative organism of sarcoidosis (7-11), as it is the only microorganism that has been isolated from bacterial cultures of sarcoidosis granulomas (7). In addition, fragments of nucleic acids of *P. acnes* have been detected in sarcoid lymph nodes by quantitative polymerase chain reactions and *in situ* hybridization (8-10). In an immunohistochemical study using a PAB antibody, Negi et al. reported a high frequency and specificity of *P. acnes* in sarcoid granulomas (11). In their analysis, PAB antibodies did not react with non-sarcoid granulomas such as tuberculosis or in sarcoid reactions caused by malignant tumors. Furthermore, findings from case reports and small clinical trials suggest that antibiotics such as tetracyclines and macrolides are effective for treating sarcoidosis (21-23), perhaps because of their anti-inflammatory and anti-microbial effects against infectious microorganisms such as *P. acnes*.

In our patient, *P. acnes* was identified in noncaseating granulomas of sarcoidosis induced by TNF- α inhibitors. It is hypothesized that latent *P. acnes* infection in the lungs and lymph nodes is activated by environmental factors, which triggers an immune response in patients with *P. acnes* al-

lergy (24). Thus, we hypothesize that among individuals with systemic immunological disorders and malignant tumors, those with latent *P. acnes* infection may show aberrant responses to drugs such as TNF- α inhibitors and immune checkpoint inhibitors and consequently develop drug-induced sarcoidosis. This hypothesis suggests that DISRs and sarcoidosis share a pathogenetic mechanism and differ only in the exogenous stimuli that trigger their development. The extrinsic factors that activate the host are distinct in DISRs and are unclear in some patients with sarcoidosis.

Conclusions

To the best of our knowledge, this is the first case in which *P. acnes* was detected in the granulomas of a patient with sarcoidosis induced by a TNF- α inhibitor. These findings suggest that *P. acnes* is a cause of sarcoidosis, even in cases induced by drugs such as TNF- α inhibitors.

Author's disclosure of potential Conflicts of Interest (COI).

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