Letter to the Editor

Yonsei Med J 2016 Jan;57(1):272-273
http://dx.doi.org/10.3349/ymj.2016.57.1.272

Yonsei Medical Journal
YMJ
pISSN: 0513-5796 · eISSN: 1976-2437

Pulmonary Sarcoidosis Induced by Adalimumab: A Case Report and Literature Review

Jae Kyeom Sim, Sung Yong Lee, Jae Jeong Shim, and Kyung Ho Kang

Division of Pulmonary, Allergy and Critical Care Medicine, Department of Internal Medicine, Korea University Guro Hospital, Seoul, Korea.

To the Editor:

Adalimumab is an anti-tumor necrosis factor-alpha (TNF-α) monoclonal antibody that is widely used in autoimmune diseases including rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease and sarcoidosis. Paradoxically, sarcoidosis can develop during treatment with adalimumab. We report an unusual case of sarcoidosis after adalimumab therapy.

A 25-year-old man with ankylsoing spondylitis started treatment with adalimumab. Initial chest radiography, tuberculin skin test and interferon gamma release assay were normal. Ten months later, abnormal opacities on chest radiography were found during the follow-up period. He was asymptomatic and appeared otherwise healthy. Tuberculin skin test and interferon gamma release assay were negative. Chest X-ray and computed tomography showed clustered small nodules, focal consolidations, some large nodules and enlarged mediastinal lymph nodes (Fig. 1A). Acid-fast bacilli stain, tuberculosis polymerase chain reaction and bacterium or fungus culture of bronchial aspirates results were all negative. Percutaneous lung biopsy was performed, and non-caseating granulomatous lesions located along lymphatic route with parenchymal inflammation were observed (Fig. 1B). Angiotensin converting enzyme was elevated to 95.7 U/L (9.0–47.0). The lesion showed partial resolution after 2 months of discontinuation of adalimumab. Hence, diagnosis of pulmonary sarcoidosis induced by adalimumab therapy was made.

Received: June 22, 2015 **Revised:** July 13, 2015
Accepted: July 13, 2015
Corresponding author: Dr. Kyung Ho Kang, Division of Pulmonary, Allergy and Critical Care Medicine, Department of Internal Medicine, Korea University Guro Hospital, Korea University College of Medicine, 148 Gurodong-ro, Guro-gu, Seoul 08308, Korea.
Tel: 82-2-2626-3028, Fax: 82-2-2626-1166, E-mail: kkhchest@korea.ac.kr

•The authors have no financial conflicts of interest.

At present, 5 types of TNF-α inhibitor are available: etanercept, infliximab, adalimumab, certlizumab pegol and golimumab. Since its first approval for rheumatoid arthritis, it has been widely used for psoriatic arthritis, ankylosing spondylitis, Crohn's disease and chronic plaque psoriasis. In addition to approved indications, TNF-α inhibitors have therapeutic effect on various diseases including sarcoidosis. Although its pathogenesis is not fully understood, TNF-α may have a role in the development of sarcoidosis. TNF-α released from alveolar macrophage was elevated in sarcoidosis,[1] and there was a positive relationship between sarcoidosis activity and TNF-α from alveolar macrophage.[2] A randomized controlled trial proved the efficacy of infliximab in sarcoidosis.[3] Currently, infliximab is preserved for refractory sarcoidosis, and the efficacy of adalimumab has also been demonstrated in a recent small study.[4] However, there have been a few cases of paradoxical occurrence of sarcoidosis during TNF-α inhibitor therapy. From a literature review, we found 59 cases of TNF-α inhibitor-induced sarcoidosis published from January 2003 to August 2014. Mean age was 47.8 years. Female to male ratio was approximately 2:1. Twenty-eight patients had rheumatoid arthritis. Mean time to onset was 21.8 months, varying from 3 weeks to 7 years. Thirty-seven cases were induced by etanercept, 9 were infliximab and 12 were adalimumab. Multiple organs were involved in several patients. Lung was the most commonly affected organ (38), followed by skin (22), and the eye (9). Fifteen patients were treated with discontinuation of TNF-α inhibitor, and 30 patients were treated with discontinuation of TNF-α inhibitor and administration of steroid. Treatment response was favorable, with 52 patients showing partial or complete resolution.

There are a few hypotheses for this paradoxical event. Macrophages or lymphocytes express TNF-α on cell membrane or release them. Monoclonal antibodies such as adalimumab or infliximab have high neutralizing potency to membranous TNF-α and cause cell lysis by activating complement. In contrast, etanercept acts preferentially on soluble TNF-α and cannot activate complement. The incomplete interruption pro-

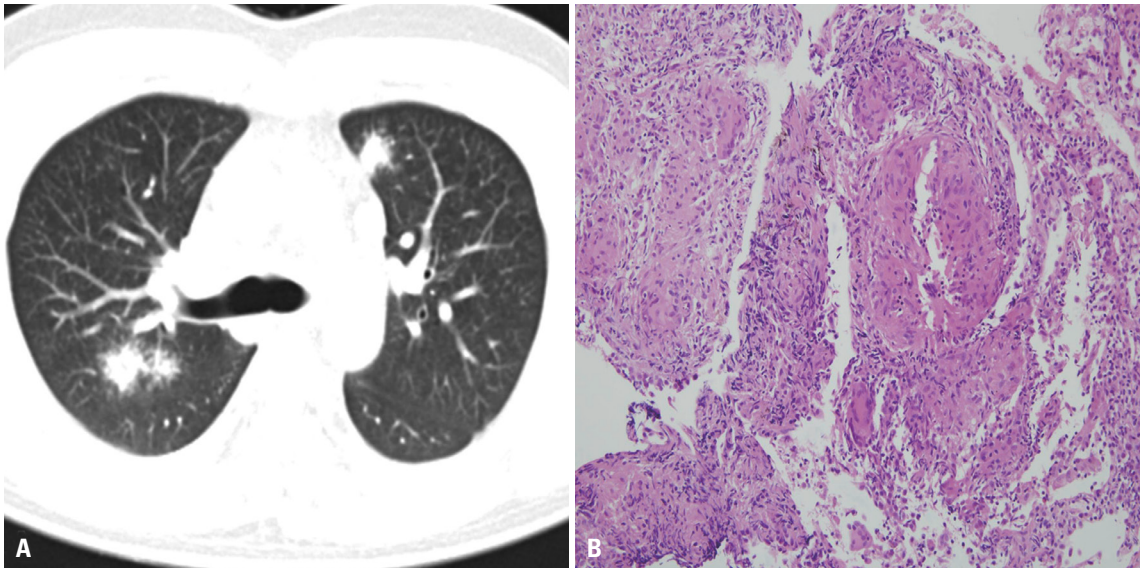

Fig. 1. (A) There are consolidation and clustered nodules at both upper lobes. (B) Multiple non-caseous granulomas are located along lymphatic route with parenchymal inflammation (H&E, original magnification ×200).

motes lymphocytes to produce more cytokines for compensation.[5] The survived lymphocytes and excessive cytokines are thought to promote sarcoidosis. This difference explains why patients treated with etanercept develop more incidents of sarcoidosis. However, it is not enough to explain sarcoidosis developed during monoclonal antibody treatment; whether it is subsequent response to suppression of TNF-α or other unknown mechanism. TNF-α inhibitor may have ability to cause immunologic disturbances, and sarcoidosis may be one of those results. Like other autoimmune diseases, complex interactions among environmental factor, genetic feature and immunologic response may contribute to the development of sarcoidosis. Eishi, et al.[6] revealed mycobacterial and propionibacterial DNA in lymph nodes of sarcoidosis patients, implying that infectious agents trigger immune response in sarcoidosis. van der Stoep, et al.[7] suggested that a hidden infection exacerbated by TNF-α inhibitor might induce sarcoidosis-like granuloma. The infrequent and paradoxical complication of TNF-α inhibitor is increasingly recognized. Nonetheless, there is a lack of plausible explanation. Further investigations will clarify the pathogenesis of sarcoidosis and the diverse effects of TNF-α inhibitor.

REFERENCES

1. Pueringer RJ, Schwartz DA, Dayton CS, Gilbert SR, Hunninghake GW. The relationship between alveolar macrophage TNF, IL-1, and PGE2 release, alveolitis, and disease severity in sarcoidosis. Chest 1993;103:832-8.
2. Ziegenhagen MW, Rothe ME, Zissel G, Müller-Quernheim J. Exaggerated TNFalpha release of alveolar macrophages in corticosteroid resistant sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 2002;19:185-90.
3. Baughman RP, Drent M, Kavuru M, Judson MA, Costabel U, du Bois R, et al. Infliximab therapy in patients with chronic sarcoidosis and pulmonary involvement. Am J Respir Crit Care Med 2006;174:795-802.
4. Sweiss NJ, Noth I, Mirsaeidi M, Zhang W, Naureckas ET, Hogarth DK, et al. Efficacy Results of a 52-week Trial of Adalimumab in the Treatment of Refractory Sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 2014;31:46-54.
5. Dinarello CA. Differences between anti-tumor necrosis factor-alpha monoclonal antibodies and soluble TNF receptors in host defense impairment. J Rheumatol Suppl 2005;74:40-7.
6. Eishi Y, Suga M, Ishige I, Kobayashi D, Yamada T, Takemura T, et al. Quantitative analysis of mycobacterial and propionibacterial DNA in lymph nodes of Japanese and European patients with sarcoidosis. J Clin Microbiol 2002;40:198-204.
7. van der Stoep D, Braunstahl GJ, van Zeben J, Wouters J. Sarcoidosis during anti-tumor necrosis factor-alpha therapy: no relapse after rechallenge. J Rheumatol 2009;36:2847-8.