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Adalimumab-induced pulmonary sarcoidosis not progressing upon treatment with etanercept

Introduction

Tumor necrosis factor alpha (TNF-α) inhibitors are used in the treatment of inflammatory rheumatologic conditions including ankylosing spondylitis (AS). In recent years, TNF-α inhibitors have also been used in the treatment of sarcoidosis [1]. However, there have been some cases of inconsistent occurrence of sarcoidosis during TNF-α inhibitor therapy. In most cases, sarcoidosis developed when etanercept was used rather than adalimumab or infliximab [2–4]. In addition, there has been a report of etanercept-induced sarcoidosis resolving with adalimumab [1]. We present the case of a patient with AS and adalimumab-induced sarcoidosis which was not aggravated by switching adalimumab for etanercept.

Anamnesis

A 26-year-old Asian man presented to the pulmonary clinic for evaluation of abnormal findings in his chest X-ray (CXR). The patient was an office clerk who had a 10-year history of smoking half a pack of cigarettes per day. He had received a diagnosis of AS and was treated with adalimumab monotherapy 10 months ago.

Clinical findings

The patient was asymptomatic and there were no signs of exacerbation of AS. The CXR showed patchy opacities on right upper and middle lung zone; the computed tomography (CT) showed a cluster of small and large nodules, focal consolidations in both the lungs, and lymph node enlargement in hilar, subcarinal, and paratracheal areas (**Fig. 1a**). The results for tuberculosis, such as tuberculin skin test, interferon gamma release assay, acid-fast bacilli (AFB) stain, and tuberculosis polymerase chain reaction were negative. No growth was observed in the bacterial (Gram staining, AFB staining) or fungal (hyphae/pseudohyphae) cultures of bronchial aspirate samples. The laboratory evaluation revealed an elevated angiotensin-converting enzyme (ACE) level of 95.7 units per liter (U/L, normal 9.0–47.0 U/L). A percutaneous lung biopsy revealed chronic non-caseating granulomatous inflammation (**Fig. 2**). No discernible microorganisms were found by Grocott's methenamine silver (GMS), periodic acid–Schiff (PAS), or AFB staining. Adalimumab therapy was discontinued owing to the concern

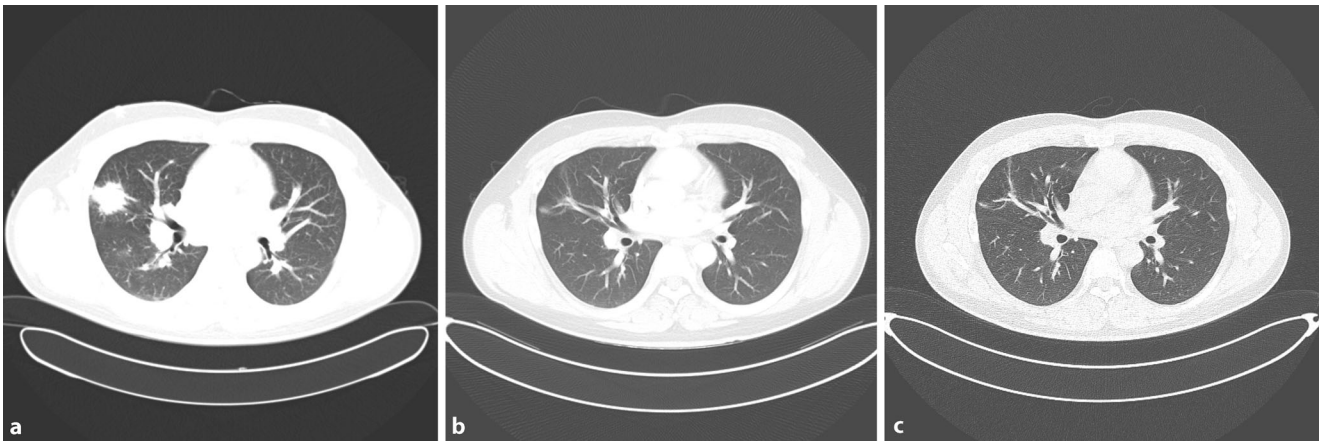

Fig. 1 ▲ Computed tomography images. **a** Image taken at the time of adalimumab treatment was discontinued. Nodules, focal consolidations in both lungs, and lymph node enlargement in hilar, subcarinal, and paratracheal areas are visible. **b** Image taken at the time of initiation etanercept treatment. Numbers of nodules and lymph nodes are decreased relative to image in (**a**). **c** Image taken 1 year after starting etanercept treatment. This image shows histologically confirmed reduction in chronic granulomatous inflammation in multifocal areas

that it could be the possible cause of granulomas.

Diagnosis

Over the next 2 months, the patient's lung lesions began to resolve, and pulmonary sarcoidosis induced by adalimumab was diagnosed.

Therapy and clinical course

After discontinuation of adalimumab, the patient was treated with a non-steroidal anti-inflammatory drug (aceclofenac), sulfasalazine (1500 mg, twice daily), methylprednisolone (2 mg, twice daily), and methotrexate (15 mg, once per week). However, he reported a gradual worsening of pain and his inflammatory markers, such as erythrocyte sedimentation rate (ESR), became elevated. His ESR increased from 19 to 79 mm/h. Fifteen months after the diagnosis of pulmonary sarcoidosis, his ACE level decreased to 26.4 U/L and the number of nodules and lymph nodes in the lungs also decreased when compared with the previous chest CT results (**Fig. 1b**). He was administered etanercept by injection and has since been maintained on etanercept for 1 year, with no recurrence of pulmonary sarcoidosis (**Fig. 1c**). His ESR decreased to 15 mm/h, and his ACE level was 45.3 U/L, which was within the normal range.

Discussion

TNF-α inhibitors have proven to be effective in the treatment of granulomatous inflammatory diseases such as sarcoidosis. Previous studies have shown that TNF-α levels increased in sarcoidosis, and it is a key cytokine in the inflammatory cascade seen in sarcoidosis [5]. Infliximab was the first drug used for the treatment of refractory sarcoidosis. Later, adalimumab and etanercept were also used for the treatment of sarcoidosis. Adalimumab is a fully human anti-TNF monoclonal antibody and has high affinity for both soluble and membrane-bound TNF receptors. Etanercept is a humanized soluble TNF receptor that mimics the naturally occurring human soluble TNF receptors and competes with these [6].

Although TNF-α blockers are effective in the treatment of sarcoidosis, about 1/2800 patients treated for inflammatory arthritis experienced a paradoxical sarcoid-like reaction [7]. In a literature review conducted up to June 2016, 64 cases of TNF-α inhibitor-induced sarcoidosis were reported. Among these, etanercept-induced sarcoidosis was the most common (41 cases), followed by adalimumab-induced sarcoidosis (14 cases), and least common was infliximab-induced sarcoidosis (9 cases). In addition, one of the cases reported that etanercept-induced sarcoidosis resolved with adalimumab treatment. Etanercept acts only on soluble TNF-α and cannot activate the complement system. Therefore, the surviving lymphocytes and excessive cytokines may promote sarcoidosis [2].

However, this case report showed that such an explanation of TNF-α inhibitor-induced sarcoidosis is not enough to account for the cause of the disease. In this report, sarcoidosis developed under treatment with adalimumab, whereas treatment with etanercept did not show recurrence of sarcoidosis. The lack of efficacy of etanercept in sarcoidosis treatment may be because it does not bind universally or avidly to membrane-bound TNF [6]. James et al. reported that etanercept was associated with treatment failure in patients with sarcoidosis, and their study was stopped early because of excessive treatment failures [8]. Although our case report did not show an improvement in active sarcoidosis when treated with etanercept, it did prevent recurrence of sarcoidosis and demonstrated that sarcoidosis was not aggravated by treatment with etanercept.

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Abstract

Tumor necrosis factor alpha (TNF-α) inhibitors effectively treat sarcoidosis, but can, paradoxically, induce sarcoidosis. The TNF-α inhibitor etanercept is most commonly associated with paradoxical sarcoidosis, which has previously been reported to be resolved by adalimumab. However, we describe the case of a patient with ankylosing spondylitis and adalimumab-induced sarcoidosis not aggravated by switching to etanercept, thus indicating that etanercept could be a treatment option for patients who develop paradoxical sarcoid-like reactions after treatment with other TNF-α inhibitors.

Keywords

Adalimumab · Etanercept · Pulmonary sarcoidosis · Tumor necrosis factor-α · Paradoxical response

Kein Fortschreiten einer Adalimumab-induzierten Lungensarkoidose unter Etanercept

Zusammenfassung

Tumor-Nekrose-Faktor-α(TNF-α)-Inhibitoren sind ein wirksames Therapeutikum der Sarkoidose, können aber paradoxerweise eine Sarkoidose auch induzieren. Der TNF-α-Inhibitor Etanercept ist am häufigsten mit einer paradoxen Sarkoidose assoziiert. Wie berichtet wurde, konnte diese mit Adalimumab kuriert werden. In dieser Kasuistik beschreiben wir jedoch den Fall eines Patienten mit ankylosierender Spondylitis und Adalimumab-induzierter Sarkoidose, die sich nach einem Wechsel zu Etanercept nicht verschlechterte. Daher könnte Etanercept eine Behandlungsoption für Patienten sein, bei denen es nach Therapie mit anderen TNF-α-Inhibitoren zu paradoxen sarkoidähnlichen Reaktionen kommt.

Schlüsselwörter

Adalimumab · Etanercept · Lungensarkoidose · Tumor-Nekrose-Faktor-α · Paradoxe Antwort

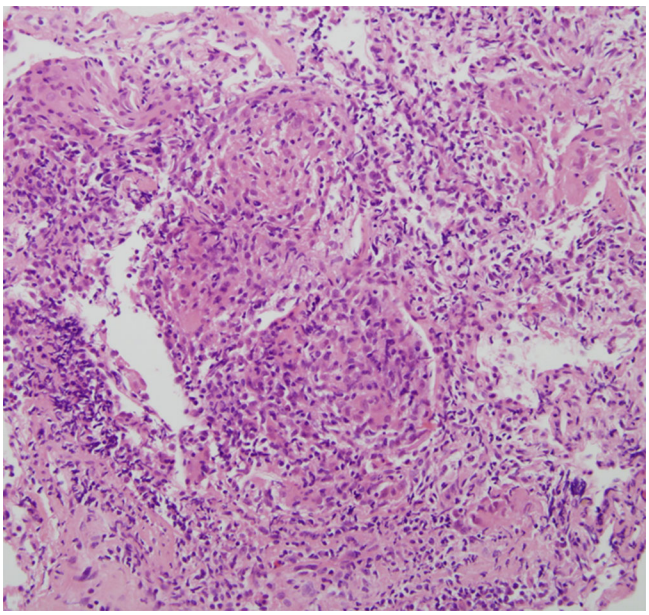

Fig. 2 ◄ Lung biopsy specimen showing multiple non-caseous granulomas located along lymphatics with parenchymal inflammation (hematoxylin and eosin stain, original magnification × 200)

Etanercept can be used as a treatment option when patients treated with other TNF-α inhibitors develop paradoxical sarcoid-like reactions. Paradoxical inflammatory response with one TNF-α inhibitor does not preclude use of another TNF-α inhibitor. Anti-TNF-α induced sarcoidosis may arise from imbalance in TNF receptor 2 (TNFR2) activation [9]. In process-induced sarcoidosis genetic factors may be associated with sarcoid-like reactions. Single nucleotide polymorphisms (SNPs) have significant associations with the response to TNF-α inhibitor [10]. In addition, other inflammatory pathways mediated by T helper cells (Th)1/Th17, interleukin (IL)-12, and IL-23 can affect sarcoidosis development [11]. Since there is a lack of plausible explanation, further studies are needed to investigate the relationship between sarcoidosis and TNF-α blocking agents. In addition, other biologic agents used in the treatment of patients with granulomatous inflammatory diseases have to be researched and personalized drug treatment needs to be established.

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Compliance with ethical guidelines

Conflict of interest. J. H. Jung, J.-H. Kim, and G. G. Song declare that they have no competing interests.

All studies on humans described in the present manuscript were carried out with the approval of the responsible ethics committee and in accordance with national law and the Helsinki Declaration of 1975 (in its current, revised form). Informed consent was obtained from all patients included in studies.

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