CLINICAL VIGNETTE

Relapsing Sarcoidosis due to TNF-α Inhibitor Therapy

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Introduction

Tumor necrosis factor-α (TNF-α) inhibitor therapies have been used for treatment of refractory sarcoidosis due to the role of TNF-α in promoting granuloma formation. However, a growing body of cases report the development of sarcoidosis and the recurrence of quiescent sarcoidosis following treatment with TNF-α inhibitors. We present a patient with relapsing quiescent pulmonary sarcoidosis after initiating treatment with etanercept for ankylosing spondylitis.

Case Presentation

A 38-year-old male with a history of kidney stones and back pain developed a chronic cough productive of green mucous. The patient's cough did not improve after treatment with antibiotics, sinus therapies, or inhaled corticosteroids. A prior CT abdomen pelvis scan that was done for evaluation of kidney stones showed extensive tree in bud pulmonary micronodularity. CT chest scan confirmed tree in bud pulmonary micronodularity in a peribronchovascular distribution (Figure 1). Fungal serologies were negative. Expectorated sputum respiratory cultures were negative for bacterial, fungal and acid fast bacilli. Bronchoscopy was done with transbronchial cryobiopsy showed non-necrotizing granulomas and negative microbiologic studies (Figure 2) and he was diagnosed with sarcoidosis. He had normal ACE levels and normal pulmonary function testing and was treated with prednisone with complete resolution of symptoms. Prednisone was tapered off after 1 year with continued resolution of cough. However, after stopping oral corticosteroids, his back pain recurred. Spine imaging showed sacroiliitis. HLA-B27 was positive. He was diagnosed with ankylosing spondylitis and started on etanercept for treatment of ankylosing spondylitis. Two months after starting etanercept, his back pain significantly improved but he had recurrence of his cough with green mucous concerning for recurrent pulmonary sarcoidosis. Repeat CT chest scan again showed tree in bud nodularity in a peribronchovascular distribution (Figure 3 left). He was diagnosed with recurrence of sarcoidosis associated with etanercept. Etanercept was discontinued and he was started on prednisone with complete resolution of symptoms. He completed another 1 year of prednisone taper with complete resolution of respiratory symptoms and improvement in imaging (Figure 3 right). However, back pain due to ankylosing spondylitis again recurred on prednisone taper. He was started on azathioprine with partial but not complete resolution of back pain. He was transitioned to secukinumab with complete resolution of back pain and no recurrence of respiratory symptoms.

Discussion

Sarcoidosis is a multisystem inflammatory disease in which noncaseating granulomas can involve almost any organ, but most commonly involves the lungs. Although the cause of sarcoidosis is unknown, granuloma formation is thought to be primarily mediated through $CD4^+$ Th cell and macrophage response to an unknown stimulus. $CD4^+$ T lymphocyte proliferation leads to a release of interleukin-2 (IL-2) and interferon-γ (IFN-γ) that eventually leads to the release of tumor necrosis factor-α (TNF-α) and IL-1β, both of which promote granuloma formation. These cells accumulate within the affected tissue, where they become increasingly organized, and form noncaseating granulomas.[1]

Oral glucocorticoid therapy is the most commonly used treatment for sarcoidosis. However, for patients with refractory disease, alternative immunosuppressive agents have been used. Methotrexate and azathioprine are the most commonly used alternate agents. In patients who are refractory to all of these, a number of other alternative immunosuppressive agents have been studied. In light of the role of TNF-α in the pathogenesis of sarcoidosis, anti–TNF-α therapies with etanercept or infliximab have been studied as potential treatments for refractory sarcoidosis with mixed results. Infliximab therapy resulted in a statistically significant improvement of 2.5% in FVC from baseline to week 24.[2] Etanercept was evaluated in a preliminary clinical trial of patients with stage 2 or 3 sarcoidosis but the trial was stopped early due to treatment failure in 11 of 17 patients.[3] These studies evaluated patients with active sarcoidosis. There have been no studies to evaluate the effect of TNF-α inhibitors in patients with quiescent pulmonary sarcoidosis.[4]

Our patient had a relapse of quiescent pulmonary sarcoidosis two months after initiating treatment with etanercept for active ankylosing spondylitis. He had complete resolution of symptoms after discontinuation of etanercept and treatment with glucocorticoid therapy. A number of published cases report development of sarcoidosis following treatment with TNF-α inhibitors.[4,5] This seems to be a paradoxic response as TNF-α is thought to promote the formulation of granulomas.

One hypothesis is that TNF-α functions to contain active inflammation in sarcoidosis, rather than itself being the primary pathogenic mediator. Louis et al suggested IFN-γ may be the primary pathogenic cytokine in granuloma formation and that etanercept may de-repress this system, resulting in a relapse of sarcoidosis in a manner similar to the activation of latent tuberculosis observed in patients treated with TNF-α inhibitors.[4] Another hypothesis is that sarcoidosis is triggered by an infectious cause and that anti-TNF-α therapy may lead to development or reactivation of an infectious agent.[5]

Figures

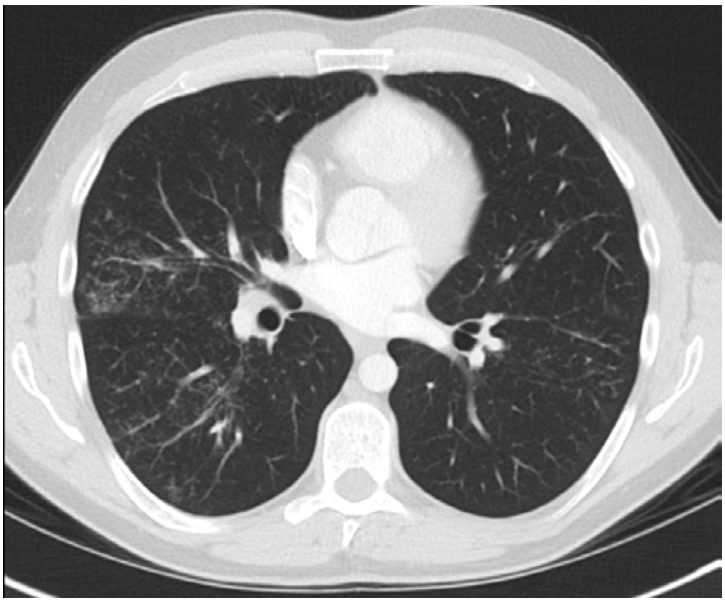

Figure 1. CT chest showing tree in bud pulmonary micronodularity in a peribronchovascular distribution.

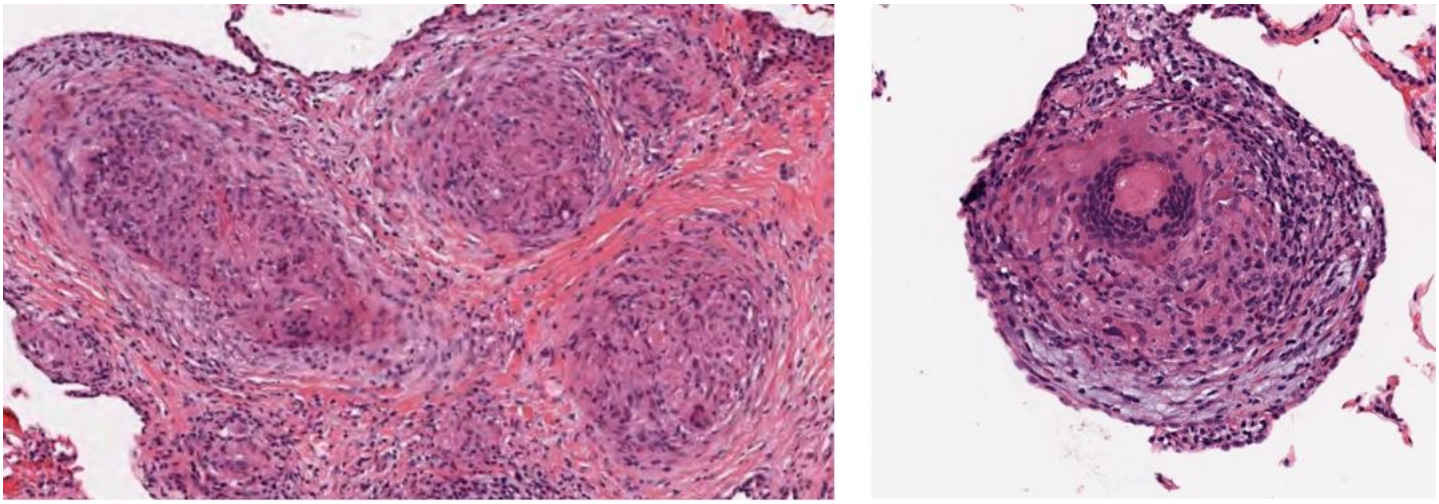

Figure 2. Surgical pathology of right lung cryobiopsy showing non-necrotizing granulomas.

Conclusion

There have been a number of case reports of the development of sarcoidosis and the recurrence of quiescent sarcoidosis following treatment with TNF-α inhibitors**.** Prompt recognition is important as discontinuation of the TNF-α inhibitor in addition to glucocorticoid therapy results in resolution of disease.

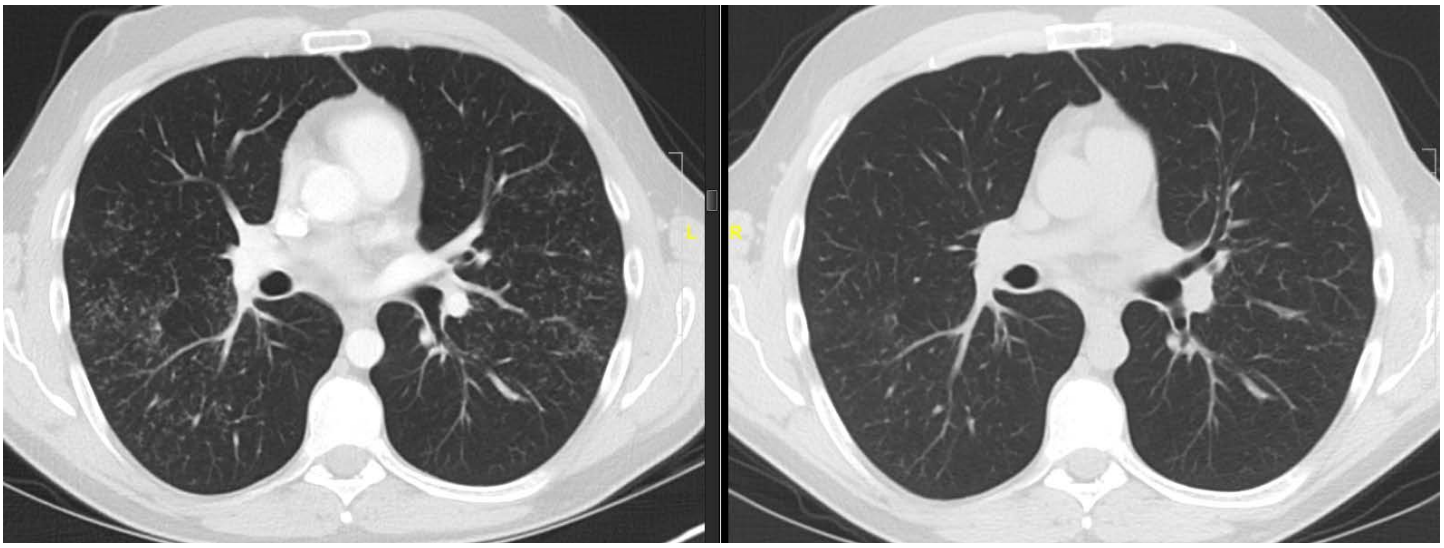

Figure 3. Left – CT chest showing tree in bud nodularity in a peribronchovascular distribution. Right - CT chest showing interval near complete resolution of peribronchovascular clustered micronodularity

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