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Letter

Pulmonary sarcoidosis and latent tuberculosis in a patient with psoriasis treated with adalimumab

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Abstract

Tumor necrosis factor (TNF) inhibitors are powerful biologic medications that have been used successfully in the treatment of a variety of inflammatory conditions, including psoriasis. Although TNF inhibitors are generally well tolerated, their use increases the risk of infections such as tuberculosis (TB), and paradoxically, they have been associated with development of sarcoidosis. We report the case of a 54-year old man with plaque psoriasis who developed a positive TB test and pulmonary sarcoidosis after 12 months of adalimumab treatment. After stopping adalimumab, his psoriasis worsened and he was started on ustekinumab and narrowband UVB, with improvement in symptoms. We provide a review of the literature and discuss treatment challenges.

Keywords: Tumor necrosis factor, TNF, psoriasis, sarcoidosis, tuberculosis, adalimumab, ustekinumab

Introduction

Tumor necrosis factor (TNF) is a pro-inflammatory cytokine, whose dysregulation is associated with the development of a number of inflammatory conditions [1]. Inhibitors of TNF are approved in the United States for the treatment of psoriasis, psoriatic arthritis, rheumatoid arthritis, Crohn disease, ulcerative colitis, ankylosing spondylitis, and juvenile idiopathic arthritis [1]. Currently, five anti-TNF agents are commercially available: infliximab, etanercept, adalimumab, certolizumab pegol, and golimumab [1].

As a class, TNF inhibitors are generally well tolerated. However, in rare cases, the use of TNF inhibitors has been associated with increased risk of infections, reactivation of latent TB, induction of auto-antibodies and lupus-like syndrome, worsening of congestive heart failure, and increased risk of malignancies, although the latter is controversial [2]. Furthermore, anti-TNF therapies have also been associated with paradoxical effects, such as exacerbation or new onset of conditions that usually improve with TNF inhibitors, including psoriasiform skin reactions, uveitis, and granulomatous diseases such as sarcoidosis [2, 3].

We present a patient with plaque psoriasis who developed a positive TB screening test and pulmonary sarcoidosis while being treated with adalimumab. We review the current literature, discuss potential pathogenesis of our patient's sarcoidosis, and discuss management challenges.

Case synopsis

We report the case of a fifty-four-year-old man with plaque psoriasis, well-controlled with adalimumab mono-therapy for 12 months. Prior to initiating adalimumab, he had been unsuccessfully treated with narrowband UVB therapy and multiple topical medications including corticosteroids, calcipotriene, and coal tar. His PASI (Psoriasis Area and Severity Index) score was 18 and 15% of his body surface area was affected. Of note, he was not a candidate for methotrexate therapy owing to chronically elevated liver function tests. On adalimumab, the patient achieved almost complete clearance of his skin disease.

After 12 months of adalimumab therapy, the patient's screening TB skin test (PPD) was found to be positive and follow-up IFN-γ-release assay (QuantiFERON-TB Gold) was also positive. Prior to initiating therapy, he had a negative QuantiFERON-TB Gold test. Chest radiography (CXR) showed left hilar opacity and he had no previous CXRs for comparison. The patient denied dyspnea, cough, hemoptysis, sputum production, chest pain, fever, chills, or weight loss. He had never received the BCG vaccine, had no known contacts with TB patients, and had no history of lung disease. His other medical conditions included type II diabetes, hypertension, and hyperlipidemia. His medications were pravastatin, benicar, olmesartan, nebivolol, aspirin, and fenofibrate. Physical examination was unremarkable. Complete blood count and comprehensive metabolic panel were normal, except for chronically elevated ALT 69 (normal 10-35 U/L). Serum ACE level was normal. Chest computed tomography (CT) scan revealed bilateral hilar and mediastinal adenopathy with perivascular nodules. Bronchoscopy with transbronchial biopsy was performed and revealed a peribronchovascular non-caseating granuloma, consistent with sarcoidosis. There was no evidence of malignancy. Biopsy samples were negative for acid-fast bacilli, and cultures were negative for mycobacteria and fungi. Adalimumab was discontinued and the patient was started on a nine-month course of isoniazid for latent TB.

After stopping adalimumab, the patient's psoriasis worsened. He was then started on ustekinumab and narrowband UVB, with partial improvement in symptoms at three-month follow-up. From a pulmonary standpoint, he remained asymptomatic and follow-up CXR was unchanged three months after stopping treatment.

Discussion

Sarcoidosis is a multisystem granulomatous disease that predominantly affects the lungs and intrathoracic lymph nodes, but can have a vast range of clinical manifestations [4]. The CXR is abnormal in 90% of patients and the most commonly visible lymph nodes are bilateral hilar nodes [4]. Serum ACE levels are elevated in approximately 60% of patients at the time of diagnosis [5]. Histopathologically, the main finding is the presence of non-caseating granulomas, the differential diagnosis of which includes infections with mycobacteria or fungi, berylliosis, hypersensitivity pneumonitis, and Wegener's granulomatosis [4].

Sarcoidal granulomas consist predominantly of aggregates of epithelioid macrophages and CD4+ T cells [4]. The majority of the CD4+ cells are of the Th1 immunophenotype, but Th17 cells are also present and are believed to contribute to the pathogenesis of the disease [6]. Interestingly, both Th1 and Th17 cells are thought to play a critical role in the pathogenesis of psoriasis and both diseases have been reported to co-occur, raising the interesting possibly that common inflammatory pathways may underlie them [7-9].

TNF is an important inflammatory mediator in sarcoidal granulomas, and TNF antagonists have been used successfully off-label to treat refractory sarcoidosis [10, 11]. However, surprisingly, TNF inhibitors have also been associated with new onset of sarcoidosis in over 30 case reports [3, 12-15]. This appears to be a class effect; infliximab, etanercept, and adalimumab have all been implicated. One French case series estimated the incidence of this adverse effect at 1/2800 [13]. The timing between anti-TNF agent introduction and granulomatosis diagnosis ranged from 1 month to 5 years and withdrawal of the agent generally resulted in resolution of clinical symptoms and radiographic findings within 12 months [12, 13]. Our patient was diagnosed with sarcoidosis after 12 months of adalimumab treatment, similar to previously reported cases. Follow-up CXR three months after stopping treatment did not reveal resolution of adenoapathy, but this is not atypical [13]. Nevertheless, although the timing is suggestive of adalimumab as the culprit in the development of our patient's sarcoidosis, we cannot exclude the possibility that sarcoidosis was present prior to initiating adalimumab or that he developed the disease due to other unknown etiologic factors.

Several mechanisms have been proposed for how anti-TNF agents may lead to sarcoidal granuloma formation. Firstly, it is possible that inhibition of TNF may modulate cytokines involved in the pathogenesis of granulomas and consequently lead to sarcoidosis [12]. A second possibility is that soluble TNF receptors (etanercept) may allow sufficient TNF activity to support

granuloma formation [16]. Lastly, TNF inhibitors may facilitate infection with an unidentified infectious pathogen responsible for causing sarcoidosis [17].

Although the precise etiology of sarcoidosis is still unknown, it is hypothesized that sarcoidosis is an immune response driven by an unidentified antigen(s) in genetically susceptible individuals [17]. Recent evidence suggests that mycobacterial products in particular may play a role in at least a subset of sarcoidosis cases [17-19]. Mycobacterial DNA has been found in sarcoidal granulomas by multiple groups [20, 21] and mycobacterium tuberculosis catalase-peroxidase (mKatG) antigen was found in sarcoidosis granulomas using both mass spectrometry and immunohistochemistry [22]. Another study demonstrated that patients with sarcoidosis have mycobacterial antigen-specific Th-17 cells peripherally and in sites of active sarcoidosis [23]. Finally, a recent randomized placebo-controlled study found that antimicrobial therapy (levofloxacin, ethambutol, azithromycin, and rifampin regimen) reduced lesion diameter and disease severity among patients with chronic cutaneous sarcoidosis [24].

An interesting aspect of our case is that our patient developed a positive PPD test while on adalimumab and was subsequently diagnosed with sarcoidosis. Because TNF inhibitors have been associated with increased risk of infections and reactivation of latent TB [2, 25-27], it is interesting to speculate that the use of adalimumab in our patient may have contributed to either new infection with TB, or re-activation of previously undiagnosed TB. In turn, TB antigens may have contributed to the pathogenesis of his sarcoidosis.

Although the precise role of anti-TNF agents in sarcoidosis remains to be established, the increasingly documented association between this class of agents and sarcoidosis poses management challenges. In particular, the question of whether it is safe to re-challenge patients with either the same or another TNF inhibitor is an area of controversy. In two cases, patients with rheumatoid arthritis (RA) developed sarcoidosis during adalimumab and etanercept treatment, respectively [28]. The agents were stopped and sarcoidosis resolved. Subsequently, the patients were re-challanged with the anti-TNF agent they originally took with no relapse of sarcoidosis [28]. In another case, a patient with RA who developed sarcoidosis while on etanercept was successfully treated with adalimumab [29]. In a French study, two patients who developed sarcoidosis switched therapy from etanercept to adalimumab and one patient switched from infliximab to etanercept, without relapse [13]. However, one patient experienced relapse after switching from etanercept to adalimumab, suggesting that re-challenge may not always be safe [13].

In our case, we chose to treat the patient with ustekinumab, a human monoclonal antibody directed against interleukins 12 and 23 [30]. There is some evidence in the literature for the efficacy of this approach. For example, ustekinumab was successfully used to treat adalimumab-induced paradoxical psoriasis in a patient with psoriatic arthritis [31]. In another case report, ustekinumab was used in a patient with Crohn disease who developed psoriasis after treatment with two anti-TNF- α drugs (infliximab and adalimumab) [32]. Nevertheless, controlled studies are needed before recommendations can be made with regards to treatment of patients who develop paradoxical reactions, such as sarcoidosis, while on TNF therapy for psoriasis and/or other conditions.

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