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CASE REPORT

Development of sarcoidosis following etanercept treatment: a report of three cases

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Abstract After over 10 years of use of tumor necrosis factor-alpha (TNF-α) inhibitors, their side effects and complications are reasonably well documented. Recently, however, granulomatous reactions and cases of complete sarcoidosis have been reported, especially in patients treated with the TNF-α receptor protein, etanercept. This is intriguing because the TNF-α antibody drugs infliximab and adalimumab are reportedly used to treat sarcoidosis. We present three patients who developed sarcoidosis while on etanercept treatment, and discuss if possible differences in cytokine profiles and T regulatory cell function in patients taking different TNF-α inhibitors may explain this paradox.

Keywords Tumor necrosis factor-alpha inhibitors · Sarcoidosis · Cytokines · T regulatory cells

Introduction

TNF-α inhibitors are efficacious for treating rheumatoid arthritis (RA) and various other chronic inflammatory diseases. Their side effects and complications have been documented for over 10 years. It was therefore somewhat unexpected that a few recent case reports described granuloma formation and complete sarcoidosis in patients treated with these drugs. Etanercept has been the culprit in most of these cases, although some have been ascribed to infliximab and adalimumab treatment [1–18]. TNF-α is thought to play a central role in the pathogenesis of sarcoidosis [19] and monoclonal antibodies against, such as infliximab, have shown promising results in the treatment of sarcoidosis [20, 21]. Paradoxically, etanercept, a TNF-α p75 soluble receptor fusion protein, has not proven to be effective [22, 23]. Because TNF-α antibody therapies differ in action compared with the soluble TNF-α receptor, questions have been raised regarding etanercept's possible unique role in promoting sarcoidosis, or whether this is a class effect for all TNF-α inhibitors. Here we present the cases of three patients who developed sarcoidosis while being treated with etanercept for ankylosing spondylitis, juvenile chronic arthritis, and RA, respectively.

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Patient 1

A 42-year-old male presented with flu-like symptoms in November 2007. He complained of swelling in the throat and parotid area associated with a runny nose, dry eyes, and dry mouth. His past medical history consisted of 30 years of ankylosing spondylitis with peripheral arthritis for which he had been treated with different DMARDs, NSAIDs, and for the last year, etanercept.

On clinical examination, his parotid glands and submandibular lymph nodes were enlarged and tender. An eye examination revealed keratoconjunctivitis sicca and a posterior uveitis. Laboratory tests showed a moderate leukocytosis, moderately raised C-reactive protein (CRP), and increased levels of angiotensin converting enzyme (ACE). Comprehensive immunological and viral serology tests did not show any abnormality. Routine cerebrospinal fluid investigations and microbiological tests, including screening for

tuberculosis, were negative. A salivary gland biopsy from the lower lip revealed necrotizing granulomas. A CT scan showed swelling of the parotid and submandibular glands bilaterally, and multiple, moderately enlarged lymph nodes in the anterior cervical chain, and in the para-aortic and mesenteric regions. Liver biopsy demonstrated granulomatous inflammatory changes and staining for tuberculosis was negative. A diagnosis of extrapulmonary sarcoidosis was made, involving the salivary and lacrimal glands, posterior uvea, liver, and lymph nodes.

Suspecting an association between the use of etanercept and the clinical syndrome, the medication was discontinued and the patient was started on azathioprine and corticosteroids. Follow-up in the outpatient clinic 2 weeks later showed resolution of the lymphadenopathy. Five months later, the patient was started on adalimumab for arthritis flare-ups with a rapid and favorable response. One month later, methotrexate was reintroduced. Six months after the diagnosis of sarcoidosis, the patient shows no signs of recurrence.

Patient 2

A 29-year-old female with juvenile chronic arthritis since the age of 6 presented with a 2-week history of bilateral parotid swelling and dryness of the eyes and mouth. She had been treated with etanercept for the last 2 years for poorly controlled arthritis. A lower lip biopsy revealed multiple granulomas consisting of epitheloid cells and some giant cells and lymphoid cells. Areas of necrosis and fibrosis were also noted (Fig. 1). A chest X-ray and Pirquet-test were normal. Routine blood tests showed mildly deranged liver function tests and raised ACE. She continued with etanercept because it provided good control of the arthritis. The sicca symptoms gradually resolved. After some time, etanercept was discontinued for conception but was reintroduced 3 years later. One year after reintroduction, dryness of the mouth, eyes, and cervical lymphadenopathy recurred. A biopsy of the salivary glands at this stage did not show any abnormality.

Patient 3

A 48-year-old female with RA for 20 years presented with a 2-month history of dyspnea upon exercise and a dry cough. She was treated with methotrexate and, for the last 3 years prior to presentation, with etanercept. Her chest X-ray showed bilateral hilar adenopathy and a transbronchial biopsy showed non-caseating granulomas consistent with sarcoidosis (Fig. 2). Bronchoalveolar lavage showed a predominance of CD4 cells compared with CD8 cells.

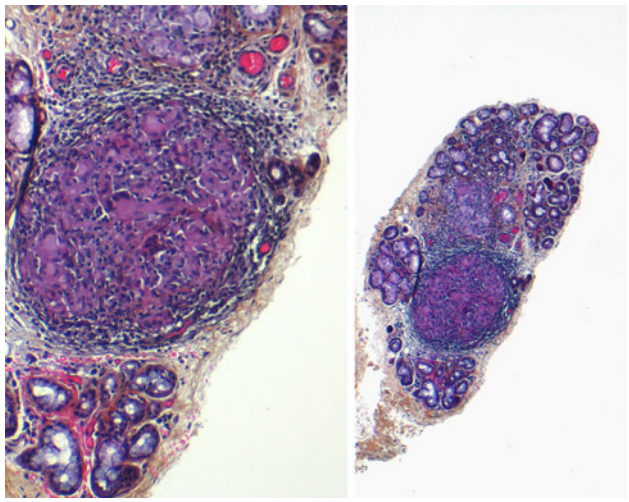

Fig. 1 Biopsy from a small salivary gland showing non-necrotizing epitheloid granulomas with a small occurrence of lymphocytes, consistent with sarcoidosis

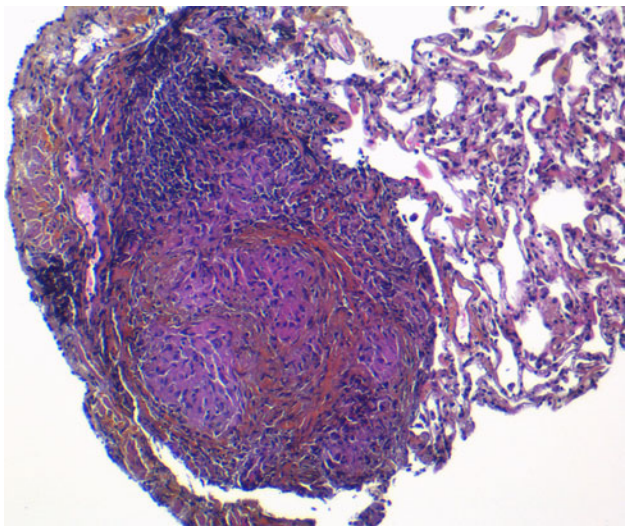

Fig. 2 Transbronchial lung biopsy showing non-necrotizing granulomas with only a small occurrence of lymphocytes, consistent with sarcoidosis

There were no malignant cells, and all microbiological tests, including tbc, were negative. Routine blood tests, including ACE and CRP, were normal. A diagnosis of sarcoidosis was made and etanercept discontinued. The patient was treated with oral prednisolone and had a favorable response and resolution of symptoms and signs. A chest X-ray 3 months later was normal.

Discussion

These case histories are consistent with previous reports of granulomatous reactions as well as frank sarcoidosis observed in patients on TNF-α antagonists [1–18]. It is

intriguing that etanercept seems more commonly associated with this phenomenon than the other TNF-α antibody drugs, and also fails to be efficacious in sarcoidosis treatment [22, 23]. Notably, our first patient did not relapse when adalimumab was introduced after etanercept. Etanercept has failed in treatment of sarcoidosis and Crohn's disease [22–24], while infliximab and adalimumab have demonstrated effect in both diseases [20, 21, 25–27]. Also the risk of reactivation of latent *Mycobacterium tuberculosis* is significantly higher for infliximab than for etanercept [28, 29]. Several explanations for these discrepancies may exist and for the possible predominance of promoting sarcoidosis during etanercept treatment.

Infliximab and etanercept differ with respect to dosing, pharmacokinetics, and binding avidity. Infliximab and adalimumab are monoclonal TNF-α antibodies whereas etanercept is a TNF-α p75 soluble receptor that binds mainly to soluble TNF-α molecules and interacts with transmembrane TNF with reduced avidity compared with infliximab**.** Infliximab binds both transmembrane TNF and soluble TNF. Clearance of etanercept is about 13 times greater than that of infliximab and adalimumab. Therefore, suppression of TNF-α is greater and more prolonged with infliximab and adalimumab [30]. Infliximab tend to achieve higher peak dose and it has been proposed that higher immediate dosing leads to intracellular suppression of TNF [31].

The granulomas in sarcoidosis consist of epitheloid-like macrophages and giant cells, surrounded by mostly $CD4^+$ T cells [32]. Cytokines, such as TNF-α, IL-2, and especially IFN-γ, appear to be of crucial importance for the formation and continuation of the granulomas [33].

T regulatory (T_{reg}) cells are important in preventing autoimmunity and are capable of suppressing proliferation and cytokine production of activated $CD4^+$ and $CD8^+$ T cells, and are found in close contact to these cells. TNF-α inhibits the suppressive function of T_{reg} cells [34]. Recent studies in RA patients suggest impaired T_{reg} cell function, and treatment with anti-TNF-α antibodies appears to restore the number and function of T_{reg} cells [35]. In sarcoidosis T_{reg} cells are down-regulated [36]. Treatment with etanercept maintains low levels of TNF-α, hence T_{reg} cells remain down-regulated to some extent and can lead to an augmented Th1 immune response, important in the pathophysiology of sarcoidosis. In contrast, treatment with infliximab inhibits TNF-α activity to a much greater extent, so T_{reg} cells are not down-regulated, leading to a more pronounced inflammatory suppression.

In addition, infliximab and adalimumab suppress IFN-γ production, whereas etanercept does not [37]. In light of the role of IFN-γ for granuloma formation these differences may be of vital importance. While infliximab more or less completely inhibits both TNF-α and IFN-γ, patients on etanercept maintain higher levels of IFN-γ as well as an incomplete elimination of TNF.

Table 1 Reported cases of sarcoidosis developing during TNF-α blocking therapy

Drug	No. of patients	Author	Year
ETA	3	Current report	
ETA	5	Daïen et al. [2]	2009
IFX	3	Daïen et al. [2]	2009
ADA	2	Daïen et al. [2]	2009
IFX	1	Josse et al. [3]	2009
ADA	1	Metyas et al. [4]	2009
IFX	1	Massara et al. [1]	2009
ADA	1	Massara et al. [1]	2009
ETA	1	Toussirot et al. [5]	2008
IFX	1	Toussirot et al. [5]	2008
ETA	1	Ishiguro et al. [7]	2008
IFX	1	Sturfelt et al. [17]	2008
ETA	1	Farah et al. [8]	2007
ETA	1	Kudrin et al. [10]	2007
ETA	1	Louie et al. [18]	2007
IFX	1	Almodovar et al. [9]	2007
ETA	2	Verschueren et al. [11]	2007
IFX	1	O'Shea et al. [12]	2006
ETA	1	González-López et al. [6]	2006
ETA	1	Phillips et al. [14]	2005
ETA	1	Hashkes et al. [13]	2003
ETA	1	Vavricka et al. [15]	2003
ETA	1	Peno-Green et al. [16]	2002

IFX infliximab, *ETA* etanercept, *ADA* adalimumab

Few other observations add to the evidence for the role of IFN-γ and TNF-α in granuloma formation. IFN-α treatment, commonly used for chronic viral hepatitis and some malignant disorders, can induce sarcoidosis and a variety of other autoimmune conditions [38]. Although the exact mechanism is unknown, administration of IFN-α increase IFN-γ and interleukin-2 production by $CD4^+$ T cells and may promote granuloma formation [39]. Furthermore, infections with *M. tuberculosis*, *Listeria monocytogenes*, and *Histoplasma capsulatum*, occur with 2- to 10-fold greater frequencies in patients treated with infliximab than in those treated with etanercept [37]. Both IFN-γ and TNF-α are essential in protecting against tuberculosis. The inability to produce IFN-γ strongly predisposes patients to tuberculosis [40]. The risk that infliximab poses with regard to reactivation of latent *M. tuberculosis* infection is therefore possibly due to the simultaneous suppression of TNF-α and IFN-γ, and may as well explain why it is effective in treatment of sarcoidosis, where the presence of both IFN-γ and TNF-α is necessary.

The effects of TNF-α antagonists for inhibition or induction of the granulomatous process is complex and unclear. If there is an increased frequency of sarcoidosis on etanercept treatment, this could be due to different cytokine profiles induced by the two groups of anti-TNF agents. On the other hand there also exist reports on granuloma formation on adalimumab and infliximab treatment. This could point to a possible class effect of all TNF-α inhibitors. However, if one considers exposure to these agents, patient years (PTY) for infliximab was 4,294,729, adalimumab 877,885, and etanercept 1,952,000 PTY per September 2009 (numbers according to companies representatives). Since etanercept accounts for 27% of PTY of all anti-TNF treatment, and 61% (20/33) of case reports are on etanercept (Table 1), this indicates some predilection for granuloma formation with this drug. Further observations will clarify this matter and will also shed light on the pathophysiology of sarcoidosis and other granulomatous disorders.

References

1. Massara A, Cavazzini L, La Corte R, Trotta F (2009) Sarcoidosis appearing during anti-tumor necrosis factor alpha therapy: a new "class effect" paradoxical phenomenon. Two case reports and literature review. Semin Arthritis Rheum 2009 14 Jan [Epub ahead of print]
2. Daïen CI, Monnier A, Claudepierre P et al (2009) Sarcoid-like granulomatosis in patients treated with tumor necrosis factor blockers: 10 cases. Rheumatology (Oxford) 48(8):865–866
3. Josse S, Klemmer N, Moreno-Swirc S, Goëb V, Lequerré T, Vittecoq O (2009) Infliximab induced skin and pulmonary sarcoidosis in a rheumatoid arthritis patient. Jt Bone Spine 76(6):718–719
4. Metyas SK, Tadros RM, Arkfeld DG (2009) Adalimumab-induced noncaseating granuloma in the bone marrow of a patient being treated for rheumatoid arthritis. Rheumatol Int 29:437–439
5. Toussirot E, Pertuiset E, Kantelip B, Wendling D (2008) Sarcoidosis occurring during anti-TNF-alpha treatment for inflammatory rheumatic diseases: report of two cases. Clin Exp Rheumatol 26:471–475
6. González-López MA, Blanco R, González-Vela MC, Fernández-Llaca H, Rodríguez-Valverde V (2006) Development of sarcoidosis during etanercept therapy. Arthritis Rheum 55:817–820
7. Ishiguro T, Takayanagi N, Kurashima K et al (2008) Development of sarcoidosis during etanercept therapy. Intern Med 47:1021–1025
8. Farah RE, Shay MD (2007) Pulmonary sarcoidosis associated with etanercept therapy. Pharmacotherapy 27:1446–1448
9. Almodóvar R, Izquierdo M, Zarco P, Javier Quirós F, Mazzucchelli R, Steen B (2007) Pulmonary sarcoidosis in a patient with ankylosing spondylitis treated with infliximab. Clin Exp Rheumatol 25:99–101
10. Kudrin A, Chilvers ER, Ginawi A et al (2007) Sarcoid-like granulomatous disease following etanercept treatment for RA. J Rheumatol 34:648–649
11. Verschueren K, Van Essche E, Verschueren P, Taelman V, Westhovens R (2007) Development of sarcoidosis in etanercept-treated rheumatoid arthritis patients. Clin Rheumatol 26:1969–1971
12. O'Shea FD, Marras TK, Inman RD (2006) Pulmonary sarcoidosis developing during infliximab therapy. Arthritis Rheum 55:978–981
13. Hashkes PJ, Shajrawi I (2003) Sarcoid-related uveitis occurring during etanercept therapy. Clin Exp Rheumatol 21:645–646
14. Phillips K, Weinblatt M (2005) Granulomatous lung disease occurring during etanercept treatment. Arthritis Rheum 53:618–620
15. Vavricka SR, Wettstein T, Speich R, Gaspert A, Bachli EB (2003) Pulmonary granulomas after tumour necrosis factor alpha antagonist therapy. Thorax 58:278–279
16. Peno-Green L, Lluberas G, Kingsley T, Brantley S (2002) Lung injury linked to etanercept therapy. Chest 122:1858–1860
17. Sturfelt G, Christensson B, Bynke G, Saxne T (2007) Neurosarcoidosis in a patient with rheumatoid arthritis during treatment with infliximab. J Rheumatol 34:2313–2314
18. Louie GH, Chitkara P, Ward MM (2008) Relapse of sarcoidosis upon treatment with etanercept. Ann Rheum Dis 67:896–898
19. Roach DR, Bean AG, Demangel C, France MP, Briscoe H, Britton WJ (2002) TNF regulates chemokine induction essential for cell recruitment, granuloma formation, and clearance of mycobacterial infection. J Immunol 168:4620–4627
20. Baughman RP, Drent M, Kavuru M, Sarcoidosis Investigators et al (2006) Infliximab therapy in patients with chronic sarcoidosis and pulmonary involvement. Am J Respir Crit Care Med 174:795–802
21. Rossman MD, Newman LS, Baughman RP et al (2006) A double-blinded, randomized, placebo-controlled trial of infliximab in subjects with active pulmonary sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 23:201–208
22. Utz JP, Limper AH, Kalra S et al (2003) Etanercept for the treatment of stage II and III progressive pulmonary sarcoidosis. Chest 124:177–185
23. Baughman RP, Lower EE, Bradley DA, Raymond LA, Kaufman A (2005) Etanercept for refractory ocular sarcoidosis: results of a double-blind randomized trial. Chest 128:47–1062
24. Sandborn WJ, Hanauer SB, Katz S et al (2001) Etanercept for active Crohn's disease: a randomized, double-blind, placebo-controlled trial. Gastroenterology 121:1088–1094
25. Brown SJ, Abreu MT (2005) Antibodies to tumor necrosis factor-alpha in the treatment of Crohn's disease. Curr Opin Drug Discov Dev 8:160–168
26. Sands BE, Anderson FH, Bernstein CN et al (2004) Infliximab maintenance therapy for fistulizing Crohn's disease. N Engl J Med 350:876–885
27. Sandborn WJ, Hanauer S, Loftus EV Jr et al (2004) An open-label study of the human anti-TNF monoclonal antibody adalimumab in subjects with prior loss of response or intolerance to infliximab for Crohn's disease. Am J Gastroenterol 99:1984–1989
28. Keane J, Gershon S, Wise RP et al (2001) Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. N Engl J Med 345:1098–1104
29. Wallis RS, Broder MS, Wong JY, Hanson ME, Beenhouwer DO (2004) Granulomatous infectious diseases associated with tumor necrosis factor antagonists. Clin Infect Dis 38:1261–1265
30. Furst DE, Wallis R, Broder M, Beenhouwer DO (2006) Tumor necrosis factor antagonists: different kinetics and/or mechanisms of action may explain differences in the risk for developing granulomatous infection. Semin Arthritis Rheum 36:159–167
31. Wallis RS, Ehlers S (2005) Tumor necrosis factor and granuloma biology: explaining the differential infection risk of etanercept and infliximab. Semin Arthritis Rheum 34:34–38
32. Iannuzzi MC, Rybicki BA, Teirstein AS (2007) Sarcoidosis. N Engl J Med 357:2153–2165
33. Ziegenhagen MW, Müller-Quernheim J (2003) The cytokine network in sarcoidosis and its clinical relevance. J Intern Med 253:18–30
34. Valencia X, Stephens G, Goldbach-Mansky R, Wilson M, Shevach EM, Lipsky PE (2006) TNF downmodulates the function of human CD4+ CD25hi T-regulatory cells. Blood 108:253–261
35. Ehrenstein MR, Evans JG, Singh A, Moore S, Warnes G, Isenberg DA, Mauri C (2004) Compromised function of regulatory T cells

in rheumatoid arthritis and reversal by anti-TNFalpha therapy. J Exp Med 200:277–285
36. Idali F, Wahlström J, Müller-Suur C, Eklund A, Grunewald J (2008) Analysis of regulatory T cell associated forkhead box P3 expression in the lungs of patients with sarcoidosis. Clin Exp Immunol 152:127–137
37. Saliu OY, Sofer C, Stein DS, Schwander SK, Wallis RS (2006) Tumor-necrosis-factor blockers: differential effects on mycobacterial immunity. J Infect Dis 194:486–492
38. Ioannou Y, Isenberg DA (2000) Current evidence for the induction of autoimmune rheumatic manifestations by cytokine therapy. Arthritis Rheum 43:1431–1442
39. Doyle MK, Berggren R, Magnus JH (2006) Interferon-induced sarcoidosis. J Clin Rheumatol 12:241–248
40. Flynn JL, Chan J, Triebold KJ, Dalton DK, Stewart TA, Bloom BR (1993) An essential role for interferon gamma in resistance to *Mycobacterium tuberculosis* infection. J Exp Med 178:2249–2254