Published in final edited form as:

Am J Kidney Dis. 2010 December ; 56(6): e17–e21. doi:10.1053/j.ajkd.2010.08.019.

Drug-Induced Granulomatous Interstitial Nephritis in a Patient With Ankylosing Spondylitis During Therapy With Adalimumab

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Abstract

Tumor necrosis factor α (TNF- α) inhibitors are used in the treatment of rheumatoid arthritis, psoriasis, psoriatic arthritis, Crohn disease, ankylosing spondylitis, and juvenile idiopathic arthritis. Use of TNF inhibitors is associated with the induction of autoimmunity (systemic lupus erythematosus, vasculitis, psoriasis, and sarcoidosis/sarcoid-like granulomas). We report a case of interstitial granulomatous nephritis in a patient with ankylosing spondylitis after 18 months of treatment with adalimumab. Previously reported cases of sarcoid-like reactions secondary to the use of TNF- α inhibitors involved the liver, lung, lymph nodes, central nervous system, and skin. Granulomatous nephritis after adalimumab treatment has not been described. Close observation of patients undergoing treatment with TNF inhibitors for evolving signs and symptoms of autoimmunity is required. Organ involvement is unpredictable, which makes correct diagnosis and management extremely challenging.

INDEX WORDS

Ankylosing spondylitis; granulomatous interstitial nephritis; sarcoidosis; tumor necrosis factor α (TNF- α) inhibitors

Tumor necrosis factor α (TNF- α) inhibitors are approved in the United States for the treatment of rheumatoid arthritis, psoriasis, psoriatic arthritis, Crohn disease, juvenile idiopathic arthritis, and ankylosing spondylitis. Off-label use of anti-TNF therapy in patients with progressive sarcoidosis is common.^{1,2}

Use of TNF- α inhibitors has been associated with induction of autoimmunity (systemic lupus erythematosus, vasculitis, and sarcoidosis).³ We report a case of interstitial granulomatous nephritis in a patient with ankylosing spondylitis after adalimumab use. Reported cases of sarcoid-like reactions secondary to the use of anti-TNF agents involved the liver, lung, lymph nodes, central nervous system, and skin.⁴ The development of renal granulomas after the use of anti-TNF agents has not been reported.

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Financial Disclosure: The authors declare that they have no relevant financial interests.

SUPPLEMENTARY MATERIALS

Note: The supplementary material accompanying this article (doi:10.1053/j.ajkd.2010.08.019) is available at www.ajkd.org.

CASE REPORT

A 42-year-old patient was admitted to the university hospital of Göttingen, Germany, because of an increase in serum creatinine level to 2.85 mg/dL (251.94 μ mol/L) 18 months after initiation of adalimumab therapy. Estimated glomerular filtration rate (eGFR) was 26 mL/min/1.73 m² (0.43 mL/s/1.73 m²) calculated using the 4-variable isotope-dilution mass spectrometry–traceable Modification of Diet in Renal Disease (MDRD) Study equation.⁵

Ankylosing spondylitis had been diagnosed 6 years before the patient's admission. His symptoms had included recurring bilateral iritis and bilateral pain of the sacroiliac joints. HLA-B27 assay results had been positive. Radiographic studies at that time had shown signs of sacroiliitis. He had been treated initially with oral ibuprofen at a dose of 600 mg once daily and sulfasalazine, 500 mg, twice daily. Sulfasalazine was stopped after 3 months because of gastrointestinal adverse events. Disease flares with pain in both ankles, cervical spine, or shoulders occurred every 5 to 6 months, during which he reported intake of up to 600 mg of ibuprofen 3 times daily. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI, a subjective measurement of disease activity with a score of 0–10, in which 10 represents the highest activity) score was calculated, with a score of 8.05 at initial presentation to his rheumatologist. Adalimumab therapy was started at a dose of 40 mg every other week 18 months before admission to our hospital because of lack of improvement with conventional therapy. Adalimumab treatment was well tolerated and resulted in a significant improvement in lower-back pain. BASDAI score improved from 8.05 to 2. Ibuprofen was taken about every 4 weeks after switching to adalimumab therapy.

At the time of admission, the patient's symptoms included mild lower-back pain and pain in the wrists and knees that occurred mainly in the early morning hours and lasted for less than 1 hour. Adalimumab therapy was discontinued at the time of admission, and the patient was advised not to use ibuprofen any longer.

Physical examination showed blood pressure of 150/90 mm Hg. There was no evidence of lymphadenopathy or lacrimal gland enlargement. The parotid glands were slightly tender to palpation without enlargement. Ophthalmic examination showed bilateral uveitis with bilateral periphlebitis.

Initial laboratory studies showed the following values: increased creatinine level, 2.85 mg/dL (251.9 μ mol/L; reference range, 0.55–1.02 mg/dL [48.6–90.2 μ mol/L]), which had been 0.86 mg/dL (76.0 μ mol/L) 3 months before admission; serum urea nitrogen, 23 mg/dL (8.21 mmol/L; reference range, 6–25 mg/dL [2.14–8.93 mmol/L]); eGFR, 25 mL/min/1.73 m² (0.41 mL/s/1.73 m²); angiotensin-converting enzyme, 21.9 IU/L (reference range, 8.3–21.4 IU/L); antinuclear antibody, positive at a titer of 1:320 (reference range, < 1:80; antinuclear antibody had not been present before the initiation of adalimumab treatment); double-stranded DNA and anti-glomerular basement membrane antibodies, negative; and C3, within the reference range. Urine examination showed no eosinophils, casts, or proteinuria.

Chest radiograph showed new bilateral hilar adenopathy (Fig S1, provided as online supplementary material) compared with the radiograph before the initiation of adalimumab therapy. Renal ultrasonography showed normal-sized kidneys with normal parenchyma.

Treatment with prednisone was initiated at a dose of 0.5 mg/kg of body weight because the diagnosis of sarcoidosis/sarcoid-like illness was suspected based on clinical grounds. The dosage gradually was decreased to a maintenance dose of 15 mg once daily. Ramipril was added at a dose of 10 mg/d because of persistently increased blood pressure.

A left kidney biopsy (Fig 1) was performed after 2 months because of deterioration in kidney function. The biopsy specimen of the renal cortex with 7 glomeruli showed normal glomerular architecture. In the interstitium, compact infiltration with mononuclear cells was seen, consisting of mostly lymphocytes and epithelioid macrophages focally organized in small well-delineated noncaseating granulomata. Within these interstitial areas, tubuli often were collapsed. In other less inflamed areas, tubules showed regular segmental differentiation. The interstitium was slightly edematous and showed a small matrix increase. Staining for acid-fast bacilli and fungi was negative.

Immunohistochemistry of glomeruli showed slight mesangial positivity for C1q and immunoglobulin M (IgM); C3, fibrinogen, IgA, and IgG were negative. Electron microscopy showed a glomerulus with normal basement membranes and regular foot processes of podocytes; there were no dense or immune deposits in the mesangium or along the glomerular basement membranes.

At 1 year of follow-up, kidney function had improved (Fig 2), creatinine level was 1.44 mg/dL (127.3 μ mol/L), serum urea nitrogen level was 16 mg/dL (5.71 mmol/L), and eGFR was calculated as 57 mL/min/1.73 m² (0.95 mL/s/ 1.73 m²). Lower-back pain and pain of the wrists and ankles flared under isolated therapy with prednisone. Finally, treatment of ankylosing spondylitis with infliximab at a dose of 5 mg/kg of body weight was initiated, and at present, kidney function remains stable after 3 infusions of infliximab, with creatinine level of 1.67 mg/dL (147.63 μ mol/L) and eGFR of 48 mL/min/1.73 m² (0.80 mL/s/1.73 m²).

DISCUSSION

Sarcoidosis is a systemic granulomatous disease of unknown cause that can affect multiple organs. About 90% of patients have granulomatous inflammation of the lung. Some patients are asymptomatic at presentation and the diagnosis is suggested by abnormal findings on chest radiographs. Recent work by Costabel et al⁶ summarized novel techniques that could help establish the diagnosis of sarcoidosis.

To our knowledge, the present case is the first of granulomatous nephritis after adalimumab therapy. We cannot definitely exclude granulomatous interstitial nephritis caused by nonsteroidal anti-inflammatory drug or sulfasalazine use because granuloma formation has been described after use of these drugs.^{7,8} Tubulointerstitial nephritis with uveitis syndrome is another possible differential diagnosis. Uveitis can occur several months before or after kidney involvement in this syndrome.⁹ However, the parotid involvement and bilateral hilar lymph node enlargement strongly suggest the diagnosis of sarcoidosis or a sarcoid-like reaction. Most reported cases of sarcoid-like reactions after treatment with TNF-blocking agents involved etanercept or infliximab, not adalimumab (Table S1 provides an overview of the published cases).^{10–28} The mechanism by which anti-TNF agents could induce sarcoidosis is not completely clear, although existing data suggest some interesting hypotheses. TNF- α and interferon α (IFN- α) frequently show evidence of cross-regulation in vitro²⁹ and in vivo³⁰ in which suppression of TNF- α leads to increased IFN- α . IFN- α has been reported to induce sarcoidosis and other autoimmune diseases, such as systemic lupus erythematosus and dermatomyositis when used as treatment for malignancy or viral hepatitis.³¹ Most individuals treated with IFN- α do not develop autoimmune disease, and those who do should have some predisposition to this reaction. A growing number of reports suggest that genetic polymorphisms associated with autoimmune disease may increase sensitivity to IFN- α or IFN- α production.^{32,33} It is possible that these same polymorphisms may be involved in abnormal immune reactions in the setting of TNF inhibition when IFN- α presumably is upregulated.

Treatment of our patient remains difficult because many agents that are helpful for the treatment of ankylosing spondylitis would likely worsen kidney function. In a recent small retrospective study, many patients with biopsyproven renal sarcoidosis maintained a certain degree of kidney failure even after treatment with steroids.³⁴ Although we hypothesize that granulomatous nephritis was induced by adalimumab in this case, infliximab therapy was started given the limited options for treatment of progressive ankylosing spondylitis. Furthermore, infliximab has been used with success to treat renal sarcoid.³⁵ Another approach would have been to rechallenge our patient with adalimumab, as reported by others,³⁶ or switch treatment to etanercept, which is a fusion protein of soluble TNF receptor and human IgG. However, there is evidence that etanercept is not effective in the treatment of sarcoidosis.³⁷

The reported number of sarcoid-like granulomas secondary to anti-TNF therapy has been increasing.⁴ It is unclear whether this phenomenon represents a class effect. We suggest that clinicians maintain a high index of suspicion for sarcoid-like illness during treatment with these agents. Infectious causes of granulomas need to be excluded before the diagnosis of sarcoidosis/sarcoid-like granulomas can be made.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Support: Dr Sweiss received funding from the Foundation for Sarcoidosis Research, Abbott, Bristol-Myers Squibb, Genentech, and Centocor for the study of biologic therapy in sarcoid.

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Figure 1.

Kidney biopsy of the patient. (A) Dense infiltration of the interstitium with mononuclear cells consisting in part of lymphocytes and epithelioid macrophages that are organized in small granulomata (arrowheads). Tubules are compressed by the interstitial inflammatory cell infiltrate. (Periodic acid–Schiff stain; original magnification, ×10.) (B) Magnification of a noncaseating granuloma with epithelioid macrophages with surrounding lymphocytes, which were T cells by immunohistochemistry (not shown). (Periodic acid–Schiff stain; original magnification, ×40.)

Figure 2.

The patient's creatinine levels, urinary protein concentration, and sequence of events during 16 months of follow-up. Prednisone treatment was begun 3 days after admission to the hospital. Kidney biopsy was performed 2 months after initial presentation. Infliximab treatment was begun 12 months after first presentation to our hospital. Follow-up shows a stable creatinine level 4 months after administration of 3 doses of infliximab (5 mg/kg body weight) with 1.67 mg/dL. There is persisting tubular proteinuria with increased levels of α_1 -microglobulin (A1M; maximum, 43 mg/L) without albuminuria. Abbreviation: Alb, albumin. Factor for converting serum creatinine in mg/dL to $\mu\text{mol/L}$, $\times 88.4$.