

Treatment of Complicated Sarcoidosis with Infliximab Anti-Tumor Necrosis Factor- α Therapy

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Background: Tumor necrosis factor- α (TNF- α) may have an important role in the clinical exacerbation of sarcoidosis.

Objective: To treat sarcoidosis with infliximab, a chimeric human-murine anti-human TNF- α monoclonal antibody.

Design: Case report.

Setting: U.S. academic medical center.

Patient: A 72-year-old woman with sarcoidosis presenting with severe protein-losing enteropathy, hypoalbuminemia, and proximal myopathy who had not responded adequately to corticosteroid therapy and whose clinical course was further complicated by acute tubular necrosis and renal failure requiring long-term hemodialysis.

Intervention: Intravenous infusion of infliximab, 5 mg/kg of ideal body weight; infusion was repeated at 2 and 6 weeks.

Measurements: Clinical response of enteropathic and myopathic symptoms and serum albumin level.

Results: Enteropathic and myopathic symptoms resolved after infliximab therapy, and the serum albumin level also improved. However, the clinical course was complicated by the development of a hypercoagulable state associated with circulating anticardiolipin antibodies, which prompted discontinuation of infliximab therapy.

Conclusions: Infliximab therapy was successful in a patient with sarcoidosis. Tumor necrosis factor- α may be an important mediator of clinical disease in sarcoidosis and could be an attractive target for therapeutic intervention. However, infliximab may cause adverse effects associated with cytokine cascade manipulation.

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Sarcoidosis is a systemic inflammatory disorder characterized by noncaseating granulomatous infiltration of any organ. The inflammatory process may be accelerated by the release of tumor necrosis factor- α (TNF- α) from resident macrophages, resulting in further recruitment of inflammatory cells (1, 2). When necessary, treatment normally includes corticosteroids, which act in part by suppressing TNF- α synthesis (3). The effectiveness of thalidomide and pentoxifylline in some cases may similarly reflect inhibitory properties of these agents on the TNF- α pathway (4).

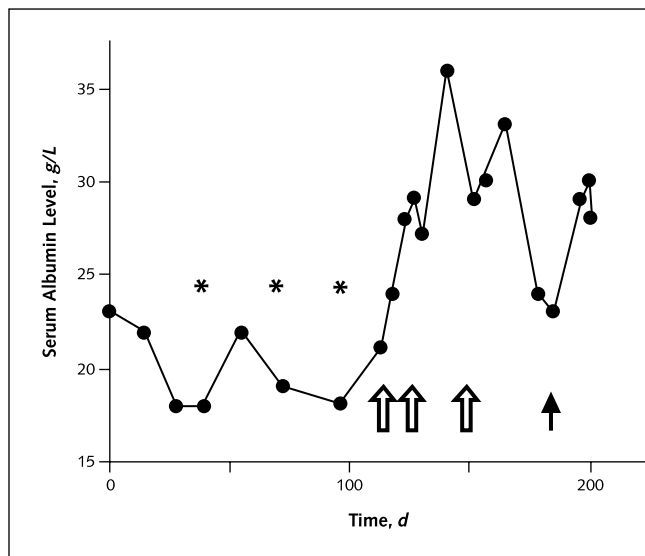
Infliximab is a chimeric monoclonal human-murine antibody against human TNF- α . It is currently approved for use only in patients with rheumatoid arthritis or Crohn disease. We describe an unusual case of sarcoidosis, manifested by severe protein-losing enteropathy and proximal myopathy, in which the patient responded dramatically to infliximab therapy. Treatment, however, was complicated by the development of hypercoagulability associated with anticardiolipin antibodies.

CASE REPORT

A 72-year-old woman presented with severe diarrhea and proximal muscle weakness. In 1975, the patient had

undergone jejunioileal bypass surgery for treatment of obesity. She subsequently developed bypass-associated wrist arthritis that necessitated antibiotic and indomethacin therapy. Since her last synovitis flare, which occurred in the mid-1980s, indomethacin therapy was continued intermittently for osteoarthritis.

The patient was in good health until June 1999, when she developed abdominal discomfort and loose stools. Results on endoscopy and colonoscopy were unrevealing. She subsequently developed persistent, frequent, watery brown diarrhea; protein-losing enteropathy; hypoalbuminemia; facial swelling; and pedal edema. Stool α_1 -antitrypsin levels were markedly elevated. Serum antigliadin IgA titers were increased slightly. However, small-bowel biopsy samples revealed normal mucosa and were inconsistent with celiac sprue, bacterial overgrowth, Whipple disease, or any other specific diagnosis. Gluten-free and lactose-free diets and empiric courses of antibiotic therapy to treat possible bacterial overgrowth were unhelpful. By December 1999, the serum albumin level was 23 g/L (Figure; day 0). The patient also reported having proximal muscle weakness, with increasing difficulty combing her hair and rising from a chair. Physical and laboratory findings at this time are outlined in the Table.

Figure. Changes in serum albumin level.

Asterisks denote intravenous methylprednisolone pulses (1.0 g/d for 3 days). White arrows denote intravenous administration of infliximab (5 mg/kg of ideal body weight). The black arrow denotes initiation of oral thalidomide, 100 mg/d.

Results on computed tomography of the chest revealed pulmonary nodules suspicious for granulomas and axillary, precarinal, and pretracheal lymphadenopathy; however, no mesenteric lymphadenopathy was seen on computed tomography of the abdomen. Mammography showed calcification of a left axillary lymph node. Perfusion abnormalities on ultrasonography in the right triceps and right vastus medialis muscles were consistent with an inflammatory myopathy; generalized atrophy was seen.

Tissue samples from axillary lymph-node and bone-marrow biopsies demonstrated noncaseating granulomas that were highly suggestive for sarcoidosis. No evidence of malignancy was seen. Stains and cultures for acid-fast bacilli and fungi were negative. Biopsy samples of the right quadriceps revealed type 2 fiber atrophy but no inflammatory or granulomatous infiltration.

Intravenous methylprednisolone, 1.0 g/d for 3 days, followed by oral methylprednisolone, 0.8 mg/kg of body weight per day, initially improved muscle strength and enzyme abnormalities. Intravenous administration of high-dose methylprednisolone was repeated 4 and 8 weeks later, but myopathic symptoms became refractory to treatment. Moreover, her enteropathy was unresponsive, and the serum albumin level decreased to 18 g/L

(Figure). Anasarca and peripheral weeping ensued. We began subcutaneous administration of methotrexate, 10 mg/wk. To treat possible bacterial overgrowth, we empirically added ciprofloxacin, 250 mg twice daily, and metronidazole, 500 mg twice daily.

Four weeks later, the patient developed acute anuric renal failure. Use of all medications except methylprednisolone was discontinued, and hemodialysis was initiated. Renal biopsy findings were consistent with acute tubular necrosis (possibly resulting from continued indomethacin use) and showed no evidence of inflammation, granulomas, or amyloid. The patient was bed bound and continued to have unremitting diarrhea.

At month 9 of the current illness, infliximab (Remicade, Centocor, Malvern, Pennsylvania), 5 mg/kg of ideal body weight, was administered intravenously. Within 2 days, the patient was able to leave her bed and rise from a chair independently. Within 1 week, she began having formed stool and was ambulating unassisted. Infliximab was administered again at 2 weeks. Within 1 month, the patient returned to work and lived independently. Her diarrhea resolved completely. The highest serum albumin level reached was 36 g/L (Figure), and her edema subsequently improved dramatically. According to computed tomography, the pulmonary nodules and intrathoracic lymphadenopathy completely resolved. Serum angiotensin-converting enzyme levels returned to normal (530 nkat/L).

Several days after receiving a third dose of infliximab at 6 weeks, the patient developed venous thrombosis at a hemodialysis catheter site and multiple necrotizing skin ulcerations on her legs. Skin biopsy samples revealed extensive thrombosis of small arteries without evidence of vasculitis. Antinuclear and anti-double-stranded DNA antibodies remained undetectable, but very high titers of anticardiolipin IgM antibodies (100 U [normally <9 U]) and slightly elevated titers of anticardiolipin IgG antibodies (17 U [normally <14 U]) were found. Levels of protein C, protein S, and anti-thrombin III were normal.

Infliximab therapy was discontinued. Soft bowel movements returned, and serum albumin level returned to 23 g/L. However, before diarrhea recurred, oral thalidomide therapy, 100 mg/d, was initiated. Stool consistency normalized, and serum albumin level increased to 30 g/L.

DISCUSSION

Infliximab was an attractive therapeutic option in our patient for several reasons. First, increasing evidence has demonstrated that TNF- α is central in the pathogenesis of sarcoidosis. Second, use of a parenteral medication was desirable because it would ensure bioavailability in the context of malabsorption. Third, many steroid-sparing medications, in particular methotrexate, presented unacceptable risks in a patient with renal failure. Finally, the effectiveness of infliximab for Crohn disease, another granulomatous disorder, provided an important precedent.

Although noncaseating granulomas remain the hallmark of sarcoidosis, their mere presence does not indicate clinically significant disease. Sarcoidosis is often diagnosed incidentally, and granulomas may occur in various tissues without clinical manifestations. The events leading from quiescent to active disease are not fully known, but TNF- α may help promote disease activity. Spontaneous release of TNF- α by alveolar macrophages is greater in patients with active disease than in patients with inactive or corticosteroid-treated disease (1, 3). Moreover, in quiescent sarcoidosis, high levels of TNF- α released from alveolar macrophages may positively predict disease progression (2).

Reports of sarcoidosis with protein-losing enteropathy have been sparse (5, 6), while the incidence of proximal myopathy is approximately 0.25% (7). Notably, no granulomas were found in small-bowel or muscle biopsy samples in our patient. One possible explanation is sampling error. Alternatively, overt granulomatous infiltration of these tissues may not be required for the observed clinical manifestations. Previous reports of protein-losing enteropathy in sarcoidosis have similarly failed to demonstrate granulomas in intestinal mucosa (5, 6). In particular, our patient's clinical profile closely resembles that of a patient described by Lindgren and colleagues (6): Both had normal small-bowel histologic findings, no mucosal or mesenteric granulomatous infiltration, and enteropathy that was refractory to corticosteroids while other disease manifestations responded. It is possible that because intestinal permeability is increased in active sarcoidosis (8), plasma proteins may leak abnormally into the intestinal lumen in susceptible patients (6). Protein-losing enteropathy has also been reported after jejunioileal bypass surgery, but blunted

Table. Physical and Laboratory Findings in Patient at the Time of Sarcoidosis Diagnosis

Physical examination
General appearance: Chronically ill but not toxic
Vital signs: Normal blood pressure, pulse, and respiratory rate; afebrile
Integument: No specific pathognomonic rashes
Head and neck: Edematous left parotid gland; no periorbital edema
Lymph nodes: 1-cm nontender left axillary node; several small, nontender cervical nodes
Chest: Normal lungs
Breasts: Normal
Heart: Normal rhythm and rate; no abnormal sounds
Abdomen: Hyperactive bowel sounds; no ascites; no hepatosplenomegaly
Extremities: Restricted wrist flexion and extension bilaterally without active synovitis; mild bipedal pitting edema
Neuromuscular: Moderately severe proximal muscle weakness in upper and lower extremities bilaterally; normal distal muscle strength
Genitourinary: Normal
Rectal: No masses; brown watery stool, negative for occult blood
Laboratory values (normal range)
Hemoglobin concentration, g/L: 108 (115–160)
Mean corpuscular volume, fL: 97 (82–100)
Leukocyte count, $\times 10^9$ cells/L: 5.5 (3.4–11.2)
Platelet count, $\times 10^9$ cells/L: 327 (150–450)
Erythrocyte sedimentation rate, mm/h: 63 (0–20)
Prothrombin time, s/International normalized ratio: 22.3 (9.3–13.0)*/2.09
Activated partial thromboplastin time, s: 36.0 (23.0–39.0)
Blood urea nitrogen level, mmol/L [mg/dL]: 4.5 [12] (2.0–9.0 [5–25])
Serum creatinine concentration, μ mol/L [mg/dL]: 80 [0.9] (40–130 [0.5–1.5])
Serum albumin level, g/L: 23 (30–50)
Serum ferritin level, μ g/L: 526 (males, 20–300; females, 20–120)
Creatine kinase level, μ kat/L: 0.33 (0.33–2.25)
Lactate dehydrogenase level, μ kat/L: 13.4 (1.33–3.75)
Aldolase level, nkat/L: 140 (0–100)
Angiotensin-converting enzyme level, nkat/L: 1430 (130–870)
Thyroid-stimulating hormone level, mIU/L: 1.7 (0.4–5.0)
Free thyroxine level, pmol/L: 14 (10–19)
24-hour urinary protein excretion, g/mol creatinine: 0.10 (<0.15)
Clostridium difficile toxin in stool: Negative
Rheumatoid factor: Negative
Antinuclear antibody: Negative
Anti-Ro/SS-A antibody: Negative
Anti-La/SS-B antibody: Negative
Intradermal mumps and Candida antigen tests: Nonreactive
Intradermal tuberculin (purified protein derivative) test: Nonreactive

* Prothrombin time returned to normal after subcutaneous administration of vitamin K.

villi and lymphocytic and plasma cell infiltration of the lamina propria are characteristic in these cases (9).

In the largest review of sarcoidosis with proximal myopathy, 16% of muscle biopsy samples revealed no granulomas (10); this percentage is similar to the percentage—20%—of negative biopsy findings in patients who have sarcoidosis without weakness (7). Therefore, overt granulomatous infiltration of muscle is neither necessary nor sufficient for myopathic symptoms to occur. Our patient's rapid response to anti-TNF- α ther-

apy indicates involvement of either TNF- α or processes closely downstream. Indeed, TNF- α , acting synergistically with interferon- γ , is directly toxic to myocytes *in vitro* (11). Because circulating monocytes express interferon- γ in active sarcoidosis (12), similar effects may occur *in vivo*. Accordingly, the absence of granulomas in bowel and muscle indicates that the putative enteropathic and myopathic effects of TNF- α may not be specific to sarcoidosis. Thus, anti-TNF- α therapy may also be useful in treating enteropathy or myopathy in other inflammatory illnesses.

Our patient's medical history included a jejunoileal bypass procedure and associated inflammatory arthritis. We speculate that the bypass provided a rich pool of microbial antigens that fueled pathogenic immunologic pathways and fomented autoimmune and inflammatory diatheses. In jejunoileal bypass-associated arthritis, changes in intestinal microflora and bacterial overgrowth are thought to promote immune complex formation and inflammatory arthritis (13). Dysregulated handling of bacterial antigens in the gut may similarly contribute to the development of sarcoidosis (8). The concept that sarcoidosis may arise in a preexisting inflammatory state amidst an altered immunologic milieu is not a novel one. For example, new-onset sarcoidosis has been observed after type 1 interferon treatment in patients with various malignant and infectious disorders (14).

The development of hypercoagulability in our patient was unexpected. The antiphospholipid antibody syndrome, a disorder of hypercoagulability associated with autoantibodies against phospholipids such as cardiolipin, may occur as a primary disorder or along with another disease (most commonly, systemic lupus erythematosus). Although antiphospholipid antibodies can occur in patients with sarcoidosis (15), the antiphospholipid antibody syndrome has been reported only once (16). It is unknown whether our patient had preexisting anticardiolipin antibodies, but she had no previous proclivity for thrombosis.

We cannot determine whether infliximab contributed to hypercoagulability in our patient. While anti-TNF- α antibody treatment may induce autoantibody production (notably anti-double-stranded DNA and, anecdotally, anticardiolipin antibodies), the development of frank autoimmune disease appears rare, and to our knowledge no cases of induced hypercoagulability have been reported (17). How TNF- α inhibition might

lead to autoantibody production is unclear. Nevertheless, deficiencies in TNF- α or TNF- α receptors appear to exacerbate murine models of autoimmunity (18, 19), suggesting that TNF- α helps maintain tolerance to autoantigens, perhaps by inducing apoptosis of autoreactive T cells (20). This hypothesis is supported by an observation (18) that activated memory T-cell proliferation is aberrantly enhanced in TNF-deficient mice, thereby potentiating autoantigen-specific T-cell reactivity.

We report successful treatment of sarcoidosis with infliximab, which directly implicates TNF- α in the pathogenesis of sarcoidosis. Thus, biological agents with specificity for TNF- α may represent a novel and more targeted treatment for sarcoidosis. However, our experience also raises concerns that such therapies may carry unforeseen adverse autoimmune and procoagulant effects. This may reflect not only the therapies themselves but also an underlying propensity for immunoreactivity in patients who are likely candidates for use of these agents. Accordingly, given the pleiotropic effects of TNF- α , carefully designed clinical trials and vigilant postmarketing surveillance of these medications are needed to determine more clearly the efficacy and safety of these agents in sarcoidosis and other inflammatory diseases.

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