

A patient's reaction to infliximab

Aaron Domm, MD

CHIEF COMPLAINT

57-year-old female complaining of fevers, weight loss, and "aching joints."

HISTORY OF PRESENT ILLNESS

The patient, previously healthy, presented to her primary care physician's office 2 years before with symptoms consistent with a flu-like syndrome. She complained of recurrent fevers up to 103° F, a dry cough, rhinorrhea, and generalized malaise. Symptomatic treatment was provided with instructions to followup if she did not improve. Over the next 2 years, the patient continued to have a multitude of seemingly unrelated symptoms. She complained of recurrent fevers, joint pains, night sweats, a generalized rash, headaches, and a weight loss of approximately 100 pounds from a state of morbid obesity. An extensive work-up followed, spanning three major teaching hospitals, with the following results.

Past Medical History

The patient has a history of mild intermittent asthma and herpes zoster.

Past Surgical History

Cholecystectomy.

Allergies

No known drug allergies. The patient is allergic to shellfish, mold, dust, and dog and cat dander.

Social History

The patient does not use tobacco products or drink alcohol. She has a pet poodle and lives in a senior center. She is now retired but worked as a tailor her entire life. She has never traveled outside the Midwest.

Family History

Brother died at the age of 46 secondary to an asthma exacerbation. Father died at a young age secondary to complications of tuberculosis.

Medications

Tylenol as needed.

Physical Examination

The patient is 57 years old, appears her stated age, and in no acute distress. She moves slowly and has difficulty rising from her chair to the examination table. The patient is febrile at 102.4° F with a pulse of 110 beats/minute and blood pressure of 110/70 mm Hg. She is non-icteric, with a supple neck and moist mucous membranes lacking any lesions or exudate. There is tenderness to palpation at the J bilaterally. A few spider angiomas are present on the chest, with no other signs of chronic liver disease. The liver spans 10 to 12 cm with a tender edge on palpation. The lungs are clear and cardiac examination reveals sinus tachycardia with no murmur or rub. A rash consisting of 0.5-cm erythematous, non-tender papules is present on her arms and hands. Strength is diminished, apparently secondary to pain at the joints on flexion and extension. The left knee joint is warm to the touch and edematous (Tables 1 and 2).

INITIAL DIAGNOSIS AND DISCUSSION

Based on the above subjective and objective information, which of the choices below is the most likely?

- A. Sarcoidosis
- B. Idiopathic granulomatous hepatitis
- C. Rheumatoid arthritis
- D. Primary biliary cirrhosis
- E. Adult-onset Still disease (AOSD)
- F. Lupus
- G. Temporal arteritis
- H. Lymphoma

After considering all possibilities, the diagnosis of AOSD is the most consistent with the clinical picture combined with the objective data. Every diagnosis in the differential is consistent with the patient's symptoms. However, some choices are easily discarded secondary to either a laboratory value or finding on physical examination. For example, rheumatoid arthritis may present with joint pains, an elevated erythrocyte sedimentation rate, fevers, weight loss, and a rash. However, the vast majority of patients will be rheumatoid factor-positive. Likewise, primary biliary cirrhosis will almost always be anti-mitochondrial antibody (AMA)-positive, lupus will be antinuclear antibody-positive, and tempo-

Department of Internal Medicine, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois.

The author has no connection with the development, production, or sale of infliximab or any medication.

Received for publication December 4, 2001.

Accepted for publication in revised form January 24, 2002.

Table 1. Laboratory Results

Lab drawn	Results	Normal range
AMA, ANA, RF, PPD, HIV	Negative	
Blood, urine, sputum cultures	No growth	
ACE	10 mmol/L	5–20 mmol/L
AST	42 units/L	5–55 units/L
ALT	48 units/L	3–50 units/L
Albumin	2.6 g/dL	3.5–5.0 g/dL
Total bilirubin	0.5 mg/dL	0.2–1.3 mg/dL
CK	39 units/L	5–200 units/L
Hemoglobin	11.2 grams/dL	12–16 g/dL
WBC	13,000/mm ³	4.5–11,000/mm ³
Platelets	487,000/mm ³	150–400,000/mm ³
Complement level	155 units/mL	CH ₅₀ 70–290 units/mL
TSH	1.12 μ U/mL	0.38–6.15 μ U/mL
ESR	>100 mm/hour	0–27 mm/hour
Ferritin	110 ng/mL	10–220 ng/mL

AMA, anti-mitochondrial antibody; ANA, antinuclear antibody; RF, rheumatoid factor; PPD, purified protein derivative; HIV, human immunodeficiency virus; ACE, angiotensin-converting enzyme; AST, aspartate aminotransferase; ALT, alanine aminotransferase; WBC, white blood cells; TSH, thyroid-stimulating hormone; ESR, erythrocyte sedimentation rate.

ral arteritis will become apparent on biopsy. None of these findings fits in our patient.

The remainder of possibilities on the differential is not as easily dismissed. Patients suffering from sarcoidosis can be febrile with an acute arthritic picture. They can even have non-caseating granulomas in the liver as our patient displays. However, the angiotensin-converting enzyme level was normal, the chest x-ray did not indicate hilar adenopathy, and hepatic granulomas are found in 2 to 10% of all liver biopsies. Further, other systemic symptoms were not present, such as lymphadenopathy and pulmonary or ocular involvement. Idiopathic granulomatous hepatitis may also present in a similar fashion. However, the diagnosis is weak, based on granulomas in liver biopsy, a finding that may be present in up to 10% of all cases. Finally, lymphoma can present with night sweats, weight loss, and arthritis. However, the patient does not display the obvious physical finding of lymphadenopathy. Therefore, with the field narrowed, AOSD is a likely choice for a working diagnosis.

AOSD is relatively rare, consisting of a systemic inflammatory process attributable to an unknown stimulus. The symptoms of AOSD are often preceded by a viral syndrome, with the symptoms sore throat, fatigue, anorexia, and arthralgias. Therefore, it is thought that an initial viral infection with a consequent circadian release of cytokines is responsible for the syndrome.¹

Pouchot et al² looked at 62 patients with AOSD and found that the disease presents with a triad of symptoms: fever, rash, and polyarthritis. All patients in this study experienced a daily temperature spike (greater than 39 °C), usually occur-

Table 2. Pertinent Films, Biopsies, and Studies

Procedure	Findings
Chest x-ray	Normal
CT of chest and abdomen	Splenomegaly; mesenteric and pericardial lymphadenopathy; otherwise normal
Total body bone scan	Moderately increased activity at the patellofemoral joints; findings consistent with osteodegenerative process
MRI of lumbar spine	Degenerative changes at L2-3, L3-4, L5-S1
Temporal artery biopsy	Normal
EMG/nerve conduction study	Normal
Liver biopsy	Non-caseating granulomas, damaged bile ducts with infiltrating polyps, eos, and numerous plasma cells present

CT, computed tomography; MRI, magnetic resonance imaging; EMG, electromyogram.

ring in the evening. Eighty-seven percent of the patients also displayed a rash on extensor surfaces of extremities, trunk, and neck. The rash usually appears during temperature spikes at night and resolves by morning.³ Arthritis is also present in 94% of patients with AOSD, affecting both the small and large joints.^{1,2} This symptom represents the greatest morbidity in patients, as it may progress into joint destruction and bony ankylosis requiring total joint arthroplasty.³ Other systemic manifestations in AOSD include lymphadenopathy, splenomegaly, hepatomegaly, and elevated liver enzymes.³ Pertinent lab values in these patients include a negative rheumatoid factor, a negative antinuclear antibody, a neutrophilic leukocytosis, an increased erythrocyte sedimentation rate, an increased C-reactive protein and elevated liver enzymes, among others.¹ The lab values, in part, help to exclude other diseases in a vast differential diagnosis that present in a similar fashion. Cush¹ proposes that the diagnosis of AOSD can be divided into probable or definite using the criteria from Table 3.

The treatment of AOSD is not unlike the treatment regimen for rheumatoid arthritis. First line of treatment includes non-steroidal anti-inflammatory drugs such as indomethacin (75 to 150 mg orally daily). This approach proves to be effective in 40 to 60% of patients afflicted.¹ The next level of care is prednisone (40 to 60 mg orally daily)¹ and finally methotrexate (7.5 to 20 mg/week). Methotrexate is used in patients who either do not find relief with steroids or need to diminish the amount of steroids that they are using.¹ All of these medications were used but eventually stopped in the patient, secondary to either minimal improvement in symptoms or unacceptable side effects.

Having exhausted the standard protocol, a relatively new addition to the treatment regimen, a tumor necrosis factor (TNF) inhibitor, was used. Infliximab, a chimeric IgG1 κ monoclonal antibody which binds TNF α , was chosen.⁴ The

Table 3. Diagnosis of AOSD

Major (one point each)	Minor (one point each)
Fever > 39°C	Onset age <35
Morbilliform rash	Arthritis
WBC > 12 + ESR > 40 mm/h	Prodromal sore throat
Negative RF and ANA	RES involvement with abnormal LFTs
Carpal ankylosis	Serositis
	Cervical or tarsal ankylosis

Probable diagnosis of AOSD: 10 points with a 12 week observation.

Definite diagnosis of AOSD: 10 points with 6 month observation.

WBC, white blood cell count; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; ANA, antinuclear antibody; LFT, liver function test.

patient responded to the first dose extremely well; daily fevers diminished, the rash improved, and she was able to climb stairs and sleep comfortably. The second dose, 2 weeks later, was also well tolerated. However, 3 weeks after receiving the second dose, she spiked a temperature to 103° F. Her fever was present when she received her third dose, which did not go as smoothly. Minutes after receiving the third dose of infliximab, the patient became tachycardic and short of breath, her blood pressure dropped, and she complained of intense pruritus and hives. These symptoms were not present before administration of the medication, and she had never experienced these acute onset symptoms in the past.

QUESTIONS

What would your clinical suspicion include on the patient's reaction? Which statement below do you feel is appropriate to describe the event? How would you proceed in diagnosing the reaction?

- An acute asthma exacerbation
- Symptomology of her AOSD
- A panic attack
- An allergic reaction
- She is suffering from a side effect of the medication

FURTHER DISCUSSION: TNF α

The treatment was immediately stopped, diphenhydramine (Benadryl, Pfizer Consumer Healthcare, Morris Plains, NJ) and oxygen were given, and the patient's symptoms improved. Neither epinephrine nor steroids were necessary. A substantial amount of research has been dedicated to the use of infliximab and medications similar to it, examining their role in treating inflammatory diseases. The ability of these medications to block TNF α is the key. TNF α plays a vital and diverse role in the inflammatory cascade. TNF α is primarily produced by macrophages, stimulated at sites of inflammation by different triggers including immune complexes, complement components, bacterial or viral products, and some cytokines.⁵ The TNF α then binds with a transmem-

brane TNF receptor, which activates a myriad of inflammatory and immunoregulatory actions in multiple cells.

Briefly, TNF α affects three major areas: the vasculature, cellular components, and multiple inflammatory mediators.⁶ TNF α modifies the vasculature by upregulating adhesion receptors, stimulating angiogenesis, and initiating a procoagulant state. TNF α also activates lymphocytes and neutrophils and induces a proliferation of fibroblasts.⁶ Further, a vast number of mediators, including pro-inflammatory cytokines (interleukin [IL]-1, IL-6, granulocyte-macrophage colony-stimulating factor), chemokines (IL-8, monocyte chemoattractant protein-1), prostaglandins, leukotrienes, and platelet-activating factor, are all upregulated or synthesized by the influence of TNF α .⁶⁻⁸ Through these actions, TNF α plays a central role in the modulation of pain, cachexia, and fever. These actions propagate arthritis by both damaging bone and cartilage and encouraging the proliferation of invasive pannus tissue.⁸

TREATMENT

The ability to specifically target and block TNF α would diminish both the symptoms and the progression of disease. Infliximab does this by binding both the soluble and transmembrane receptors, competitively downregulating the harmful actions of TNF α . Infliximab has been proven to decrease the pain and structural damage associated with inflammation in Crohn disease.^{4,9} Although it is not yet indicated for rheumatoid afflictions, the idea and the results have been the same.^{10,11} A study by Tak et al⁸ examined the response in 10 patients with rheumatoid arthritis after receiving monoclonal antibody to TNF α . The study found a significant decrease in both inflammatory cell migration and inflammatory cytokines, as well as an improvement in clinical symptoms.

However, as with any medication, potential side effects accompany any benefit gained. There are three major side effects presented in the literature. First, the risk of infection is obviously increased, as a vital portion of the body's defense system is impaired.⁴ *Listeria monocytogenes* and *Mycobacterium* have been specifically singled out as a threat in patients taking infliximab.⁶ Second, a number of patients develop a lupus-like syndrome with antibodies to double-stranded DNA. Last, the patient runs the risk of developing antibodies to the medication, causing an immediate hypersensitivity reaction when the drug is administered.⁴⁻⁶

In our patient, all three side effects are arguably possible. The patient's immune system may have been weakened by two previous doses of infliximab, allowing a microbe to flourish. In addition, the patient may have formed autoantibodies experiencing an acute lupus-like reaction. However, the symptoms at the time—immediate, intense pruritus, and shortness of breath with a tightening in the throat—do not really coincide with either of these theories. The most likely explanation for the chain of events is that our patient had an acute anaphylactic reaction to infliximab because of antibodies that formed against the medication.

The challenge for proof of this theory lies in the fact that these treatments are relatively new. Specific diagnostic testing for antibodies to the medication is not available. However, a key point in understanding a patient's reaction to the medication is that there are degrees to which the monoclonal antibodies are foreign to the human system. Murine (mouse-derived) antibodies are more immunogenic than chimeric antibodies (derived from multiple species). In turn, chimeric antibodies are more immunogenic than antibodies derived solely from humans. Infliximab is a chimeric antibody composed of human constant and murine variable regions.⁴ Therefore, there is a chance that the patient formed antibodies to the murine region which would not have become clinically evident until the second or third exposure.

To reach a diagnosis, the patient underwent both skin prick and intradermal testing (0.02 mL each at 1:10 dilution in saline) using mouse, hamster, guinea pig, and an aliquot of infliximab. Both the mouse and the infliximab produced pronounced erythema and a wheal at 30 minutes after injection. This most likely represents an activation of Fc- γ receptor positive cells by immunoglobulin G to mouse antigen present in the infliximab. The antibodies, now present in our patient after previous infliximab dosing, could easily have caused an anaphylactic reaction. After reviewing the literature, our patient's reaction does not appear to be an isolated case.^{4,6,9,10,12} Although allergic reactions to these medications are rare and somewhat counterintuitive, anaphylactic precautions should still be taken before administration.

FINAL DIAGNOSIS

Anaphylaxis to infliximab in a patient with AOSD.

REFERENCES

1. Cush JJ. Adult-onset Still's disease. *Bull Rheum Dis* 2000;49:1–4.
2. Pouchot J, Sampalis JS, Beaudet F, et al. Adult Still's disease: manifestations, disease course, and outcome in 62 patients. *Medicine* 1991;70:118–136.
3. Koopman WJ. *Arthritis and Allied Conditions*, 13th edition. Philadelphia: Williams and Wilkins, 1997:1063–1065.
4. Schreier N, Nissen D, editors. *Mosby's 2001 Medical Drug Reference*. St. Louis, MO: Mosby Year-Book, 2001.
5. Arend WP, Dayer JM. Inhibition of the production and effects of interleukin-1 and tumor necrosis factor- α in rheumatoid arthritis. *Arthritis Rheum* 1995;38:151–160.
6. Kavanaugh A. Anti-tumor necrosis factor- α , monoclonal antibody therapy for rheumatoid arthritis. *Rheum Dis Clin North Am* 1998;24:593–614.
7. Hollander AP. Criteria for identifying mediators of tissue damage in human autoimmune diseases. *Autoimmunity* 1991;9:171–176.
8. Tak PP, Taylor PC, Breedveld FC, et al. Decrease in cellularity and statement of adhesion molecules by anti-tumor necrosis factor- α monoclonal antibody treatment in patients with rheumatoid arthritis. *Arthritis Rheum* 1996;39:1077–1081.
9. Hyams J, Markowitz J, Wyllie R. Use of infliximab in the treatment of Crohn's disease in children and adolescents. *J Pediatr* 2000;137:192–196.
10. Maini RN, Breedveld FC, Kalden JR, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor- α monoclonal antibody treatment in patients with rheumatoid arthritis. *Arthritis Rheum* 1996;39:1077–1082.
11. Taylor P, Peters M, Paleolog E, et al. Reduction of chemokine levels and leukocyte traffic to joints by tumor necrosis factor- α blockade in patients with rheumatoid arthritis. *Arthritis Rheum* 2000;43:38–47.
12. Brandt J, Haibel H, Cornely D, et al. Successful treatment of active ankylosing spondylitis with the anti-tumor necrosis factor- α monoclonal antibody infliximab. *Arthritis Rheum* 2000;43:1346–1352.

Requests for reprints should be addressed to:

Aaron Domm, MD

Department of Internal Medicine

Rush Presbyterian-St. Luke's Medical Center

1650 W. Harrison Street

Chicago, IL 60612

E-mail: aarondomm@yahoo.com