

## TUBERCULOSIS ASSOCIATED WITH INFLIXIMAB, A TUMOR NECROSIS FACTOR $\alpha$ -NEUTRALIZING AGENT

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### ABSTRACT

**Background** Infliximab is a humanized antibody against tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) that is used in the treatment of Crohn's disease and rheumatoid arthritis. Approximately 147,000 patients throughout the world have received infliximab. Excess TNF- $\alpha$  in association with tuberculosis may cause weight loss and night sweats, yet in animal models it has a protective role in the host response to tuberculosis. There is no direct evidence of a protective role of TNF- $\alpha$  in patients with tuberculosis.

**Methods** We analyzed all reports of tuberculosis after infliximab therapy that had been received as of May 29, 2001, through the MedWatch spontaneous reporting system of the Food and Drug Administration.

**Results** There were 70 reported cases of tuberculosis after treatment with infliximab for a median of 12 weeks. In 48 patients, tuberculosis developed after three or fewer infusions. Forty of the patients had extrapulmonary disease (17 had disseminated disease, 11 lymph-node disease, 4 peritoneal disease, 2 pleural disease, and 1 each meningeal, enteric, paravertebral, bone, genital, and bladder disease). The diagnosis was confirmed by a biopsy in 33 patients. Of the 70 reports, 64 were from countries with a low incidence of tuberculosis. The reported frequency of tuberculosis in association with infliximab therapy was much higher than the reported frequency of other opportunistic infections associated with this drug. In addition, the rate of reported cases of tuberculosis among patients treated with infliximab was higher than the available background rates.

**Conclusions** Active tuberculosis may develop soon after the initiation of treatment with infliximab. Before prescribing the drug, physicians should screen patients for latent tuberculosis infection or disease. (N Engl J Med 2001;345:1098-104.)

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**T**HE role of tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) in the human immune response to tuberculosis remains unclear. This cytokine may be responsible for some of the clinical manifestations of tuberculous disease, including weight loss, night sweats, and tissue destruction.<sup>1,2</sup> Yet in animal models, TNF- $\alpha$  plays a central part in the host response against tuberculosis,<sup>3,4</sup> including granuloma formation and containment of disease.<sup>5,6</sup> Antibodies against TNF- $\alpha$  cause a reactivation of tuberculosis in a mouse model of latent infection.<sup>7</sup> Unlike interferon- $\gamma$ <sup>8</sup> and interleukin-12,<sup>9</sup> TNF- $\alpha$  has not been shown to have a protective role in the human immune response to mycobacteria.

Infliximab (Remicade) is a humanized monoclonal antibody against TNF- $\alpha$  that is approved in the United States and elsewhere for the treatment of rheumatoid arthritis and Crohn's disease.<sup>10,11</sup> Infusions of infliximab can be administered in a single dose, a monthly regimen, or on day 0, day 14, day 42, and then every 8 weeks. The half-life of infliximab is 10 days,<sup>12</sup> and its biologic effect persists for up to 2 months. The Food and Drug Administration (FDA) approved infliximab in 1998 for use in patients who do not have a response to other antiinflammatory agents.<sup>13</sup> Approximately 147,000 people throughout the world have received the drug; in the United States, 45,000 patients have received it for rheumatoid arthritis and 76,000 for Crohn's disease (Table 1). One case of tuberculosis after infliximab therapy was reported in a clinical trial.<sup>14</sup> We evaluated the clinical pattern of disease and the interval between the initiation of infliximab therapy and the onset of disease in 70 reported cases of tuberculosis in patients treated with infliximab. We compared the rate of reported tuberculosis in this group with available data on background incidence rates. The association of this disease in humans with decreased TNF- $\alpha$  activity suggests that the cytokine has a key role in the control of latent tuberculosis.

### METHODS

The FDA monitors the safety of newly licensed products, such as infliximab. Data from the FDA's Adverse Event Reporting System (AERS) were reviewed for reports of tuberculosis with infliximab from its licensure in 1998 through May 29, 2001. AERS receives spontaneous reports of suspected adverse drug reactions through the MedWatch program<sup>15</sup> and from pharmaceutical manufacturers. The vast majority of reports are submitted by health care providers, who are sometimes contacted for additional information. Reports to the AERS may involve any time interval between the administration of the drug and the suspected reaction. Further details are available at <http://www.fda.gov/cder/aers/>. The current collaborative study was undertaken after two of us treated the index patient, in whom tuberculosis developed after treatment with infliximab for Crohn's disease.

Patients were included in the study if during or after treatment with infliximab, they had received a diagnosis of tuberculosis on the basis of clinical, radiologic, and laboratory findings. We sought evidence in each case report of preexisting latent infection with *Mycobacterium tuberculosis*.

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**TABLE 1.** CUMULATIVE NUMBERS OF PATIENTS TREATED WITH INFlixIMAB OR ETANERCEPT, ACCORDING TO LOCATION AND INDICATION.\*

DRUG	UNITED STATES	OTHER COUNTRIES
	no. of patients	
Infliximab	121,000	26,000
Crohn's disease	76,000	NA
Rheumatoid arthritis	45,000	NA
Etanercept	95,493	6,638

\*Data, provided by the manufacturers, are for all patients who had received infliximab as of March 30, 2001, and for all those who had received etanercept as of January 31, 2001. NA denotes not available.

*bacterium tuberculosis* (i.e., a prior positive tuberculin skin test). Lung-tissue samples from our index patient were compared with archival lung tissue from a patient with tuberculosis who had not received an anti-TNF- $\alpha$  agent. Tissue samples were stained with hematoxylin and eosin, and the terminal deoxynucleotidyl transferase-uridine triphosphate nicked-end labeling method (ApoTag kit, Intergen, New York) was used to identify apoptotic cells according to the manufacturer's protocol.

## RESULTS

Seventy patients were reported to have tuberculosis during or after infliximab therapy, including the index patient. Their ages ranged from 18 to 83 years (median, 57) (Table 2). Forty-five of the patients were women. Forty-seven patients were taking the drug for rheumatoid arthritis, 18 for Crohn's disease, and 5 for other types of arthritis. The median interval from the start of treatment with infliximab until the development of tuberculosis was 12 weeks (range, 1 to 52). The distribution of cases according to the interval between the initiation of treatment and the development of tuberculosis is shown in Figure 1.

Fifty-five patients were reported to have received one or more other immunosuppressive medications, including corticosteroids (45 patients), methotrexate (35), azathioprine (6), and cyclosporine (1). Five patients were using antiinflammatory agents, such as mesalamine and indomethacin, before tuberculosis developed. Of 11 corticosteroid-treated patients in the United States for whom data were available, 9 were taking doses of prednisone that did not exceed 15 mg per day. The doses of methotrexate ranged from 10 to 20 mg per week. More than half of the patients (56 percent) had extrapulmonary tuberculosis, and approximately one quarter had disseminated tuberculosis (Table 2). Other manifestations of extrapulmonary tuberculosis included lymph-node disease (in 11 patients), peritoneal disease (in 4), pleural disease (in 2), meningeal disease (in 1), enteric disease (in 1), paravertebral disease (in 1), bone disease (in 1), genital disease

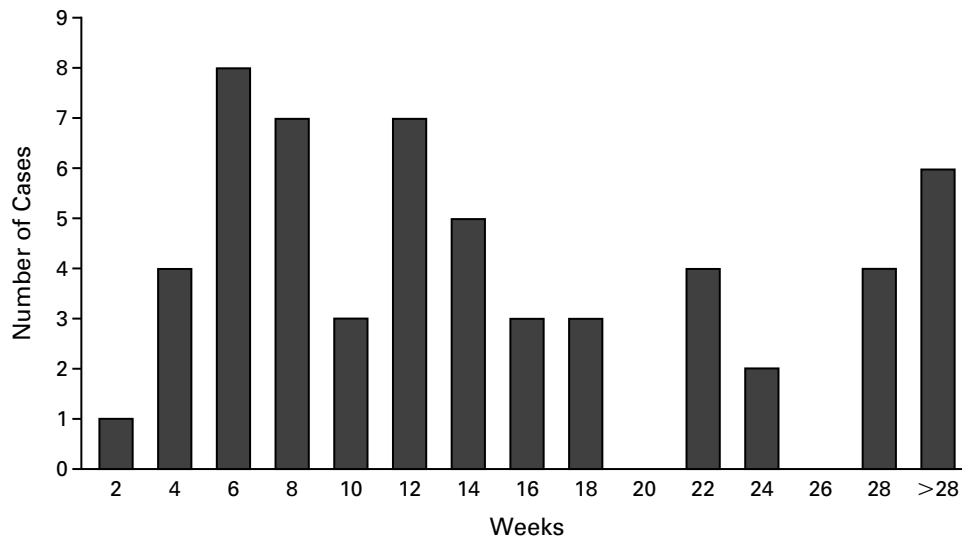
**TABLE 2.** CHARACTERISTICS OF 70 PATIENTS WITH TUBERCULOSIS AFTER INFlixIMAB THERAPY.

CHARACTERISTIC	VALUE
Age — yr	
Range	18–83
25th percentile	39
Median	57
75th percentile	67
Indication — no. (%)	
Crohn's disease	18 (26)
Rheumatoid arthritis	47 (67)
Juvenile rheumatoid arthritis	2 (3)
Ankylosing spondylitis	2 (3)
Behçet's disease	1 (1)
Recent immunosuppressant use — no. (%)	55 (79)
Methotrexate alone	6 (9)
Methotrexate plus corticosteroids	28 (40)
Corticosteroids alone	14 (20)
Azathioprine plus corticosteroids	3 (4)
Other individual or combined immunosuppressants	4 (6)
Not reported	15 (21)
Interval between first dose and diagnosis — wk*	
Range	1–52
25th percentile	8
Median	12
75th percentile	22
No. of doses*	
Range	1–9
25th percentile	2
Median	3
75th percentile	3
Clinical manifestation of disease — no. (%)	
Pulmonary	22 (31)
Extrapulmonary, not disseminated	23 (33)
Extrapulmonary, disseminated	17 (24)
Not reported	8 (11)
Method of diagnosis — no. (%)	
Culture	40 (57)
Biopsy or sputum smear for acid-fast bacilli*	16 (23)
Polymerase-chain-reaction assay	2 (3)
Not reported	12 (17)
Recent exposure to tuberculosis — no. (%)	2 (3)
Country or region of report — no. (%)	
United States	17 (24)
Europe	45 (64)
Spain	10
Italy	8
France	7
Other European countries	20
Other	8 (11)

\*Reports were not counted in this category if a culture or the polymerase-chain-reaction assay was positive.

(in 1), and bladder disease (in 1). Thirty-three of the 70 patients underwent a biopsy to confirm the diagnosis of tuberculosis; biopsy specimens were from a lung (in 12 patients), a lymph node (in 11), the peritoneum (in 3), enteric tissue (in 2), the pleura (in 1), bone marrow (in 1), the liver (in 1), a paravertebral mass (in 1), and the bladder (in 1).

Two reports noted possible recent exposure to tuberculosis. Eight patients had a history of tuberculosis infection or disease. Most of the 70 reports (91 percent) were from countries with a low incidence of tu-



**Figure 1.** Time from the Initiation of Infliximab Therapy to the Diagnosis of Tuberculosis. Data were available for 57 patients, most of whom had received monthly infusions of infliximab.

berculosis (less than 20 cases per 100,000 population per year).<sup>16</sup> On the basis of reports to the AERS, the estimated rate of tuberculosis among patients with rheumatoid arthritis in the United States who have received infliximab therapy within the previous year is 24.4 cases per 100,000. The background rate of tuberculosis in patients with rheumatoid arthritis in the United States was assessed in a recent study with active follow-up, which found one case of tuberculosis in 10,782 geographically dispersed patients with rheumatoid arthritis who were followed prospectively for approximately 18 months.<sup>17</sup> On the basis of these data, the background rate of tuberculosis in patients with rheumatoid arthritis in the United States is 6.2 cases per 100,000 per year (95 percent confidence interval, 0.6 to 34.0). Background rates of tuberculosis among patients with Crohn's disease and among patients with rheumatoid arthritis in Europe are not available for comparison with the case rates associated with infliximab therapy. Five of the 17 patients in the United States who had tuberculosis (29 percent) were immigrants, but all 5 had lived in the United States for 10 years or longer. Of the approximately 18,000 cases of tuberculosis reported in the United States in 1999, about 44 percent were in foreign-born persons.<sup>18</sup>

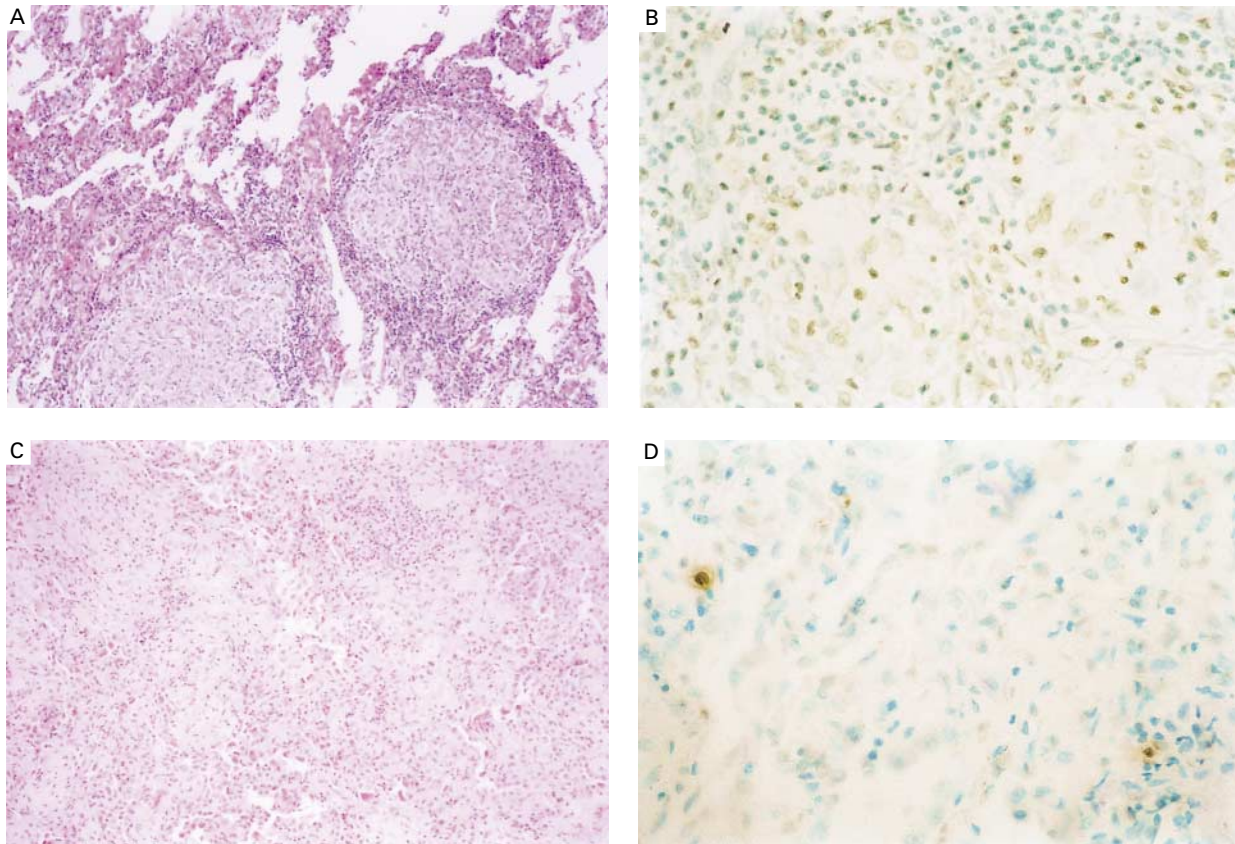
Patients received antituberculosis medication, and infliximab treatment was stopped after the diagnosis of tuberculosis had been made. Twelve patients subsequently died, and at least four of these deaths appear to have been directly related to tuberculosis. Other serious opportunistic infections have been reported in patients treated with infliximab, but the frequency of

tuberculosis exceeds that of other infections. Twelve patients treated with infliximab had listeriosis, nine had *Pneumocystis carinii* pneumonia, seven had histoplasmosis, six had aspergillosis, and seven had severe candida infections. No coinfection with the human immunodeficiency virus (HIV) has been reported.

The index patient was a 68-year-old man with Crohn's disease in whom pulmonary tuberculosis developed seven weeks after he had received a single dose of infliximab. Shortness of breath was the first symptom. A thoracic computed tomographic (CT) study suggested the presence of new pulmonary fibrosis (a previous thoracic CT study had shown no abnormalities). Histopathological examination of a specimen from an open-lung biopsy showed idiopathic pulmonary fibrosis with lymphocyte infiltration; no granulomas were present (Fig. 2C). Sputum cultures subsequently grew *M. tuberculosis* on three separate occasions, although acid-fast bacilli were not seen in the biopsy specimen. TNF- $\alpha$ -mediated apoptosis has been shown to occur after infection with *M. tuberculosis*,<sup>19</sup> and extensive macrophage apoptosis is a feature of the normal granulomatous response to tuberculosis (Fig. 2A and 2B).<sup>19-22</sup> There was little apoptosis in the lung specimen from the index patient (Fig. 2D). Caseating granulomas were described in the biopsy specimens from some of the other patients.

## DISCUSSION

Our data suggest an association between treatment with infliximab and the development of tuberculosis. Although passive surveillance data are often insufficient to prove a causal relation between an adverse event and



**Figure 2.** Photomicrographs of Lung Specimens from a Patient with Tuberculosis Who Did Not Receive Infliximab (Panels A and B) and the Index Patient with Tuberculosis Who Did Receive Infliximab (Panels C and D).

The specimen from the patient who did not receive infliximab shows well-formed granulomas with negligible overt necrosis (Panel A; hematoxylin and eosin,  $\times 100$ ). A photomicrograph of a granuloma at a higher magnification shows moderate-to-marked apoptosis, as demonstrated by the terminal deoxynucleotidyl transferase–uridine triphosphate nicked-end labeling (TUNEL) reaction. Cells stained brown are positive for apoptosis, and cells with blue nuclei, which are stained with the methyl-green counterstain, are normal (Panel B,  $\times 400$ ). The specimen of lung parenchyma from the patient who received infliximab shows prominent interstitial fibrosis and lymphoid inflammation, without granulomas (Panel C, hematoxylin and eosin,  $\times 100$ ). TUNEL analysis shows minimal apoptosis (Panel D,  $\times 400$ ).

a drug, we believe this association is not coincidental, because of the large number of reports of tuberculosis in close temporal association with the initiation of treatment and the increased rate of tuberculosis among patients treated with infliximab, as compared with available data on background rates. In addition, data from *in vitro* investigations,<sup>23,24</sup> as well as a mouse tuberculosis model,<sup>3-5,7,25</sup> link susceptibility to tuberculosis with decreased TNF- $\alpha$  activity.

We reviewed the clinical and laboratory findings in 70 cases of tuberculosis that developed after the initiation of treatment with infliximab. The pattern of tuberculous disease was unusual. The majority of the patients (56 percent) had extrapulmonary tuberculosis, and 24 percent had disseminated disease — forms of tuberculosis that are associated with marked immunosuppression. In contrast, among cases of tuberculo-

sis that are not associated with HIV infection, approximately 18 percent are manifested as extrapulmonary disease, and disseminated disease accounts for less than 2 percent.<sup>26</sup> The unusual manifestations of tuberculosis in this group of 70 cases may have made the diagnosis uncertain (as reflected by the large number of biopsies performed to establish the diagnosis); delays in the diagnosis may have contributed to morbidity and mortality. The available data suggest that the patients who survived recovered from their infections after the withdrawal of infliximab and the administration of appropriate chemotherapy for tuberculosis.

We do not have complete information about the status of these patients with respect to tuberculous infection before they received infliximab, but it is likely that most patients had reactivation disease, in view of their age (median, 57 years), the small number with report-

ed recent exposure to tuberculosis, and the low incidence of tuberculosis in the countries from which the reports were received.<sup>27,28</sup> That only eight reports noted a history of tuberculosis infection or disease is not surprising, since medical information from the remote past is frequently lacking, particularly in passive surveillance reports. Given the key role of TNF- $\alpha$  in the innate immune response to tuberculosis, patients receiving treatment with infliximab are probably also susceptible to disease after primary infection and exogenous reinfection with *M. tuberculosis*.

Foreign-born persons were not overrepresented in the U.S. reports, and all such persons had been living in the United States for more than 10 years. Persons who move to the United States have a high incidence of tuberculosis for the first five years.<sup>29</sup> With time, however, the incidence declines and approaches that in the general population. It is also not surprising that most of the reports came from countries with a low incidence of tuberculosis, because infliximab is an expensive treatment<sup>12</sup> that is rarely available in poor countries, where tuberculosis is most prevalent.

The recent use of other immunosuppressive drugs and systemic illness in infliximab-treated patients may increase the risk of a variety of opportunistic infections, including fungal infection,<sup>30</sup> but tuberculosis was reported much more frequently than other opportunistic infections. Tuberculosis is not associated with the use of prednisone at doses of 15 mg or less,<sup>29</sup> and the cytotoxic agents and low doses of corticosteroids used in this group of patients have not been associated with tuberculosis in patients with rheumatic diseases<sup>31</sup> or asthma.<sup>32,33</sup>

Another agent that neutralizes TNF- $\alpha$  is etanercept, which has been used, often along with other immunosuppressive medications, in the treatment of approximately 102,000 patients with rheumatoid arthritis throughout the world (Table 1). Etanercept is a fusion protein that binds free TNF- $\alpha$  using the extracellular or soluble portion of tumor necrosis factor receptor 2 (TNFR2) coupled with an Fc moiety.<sup>34</sup> Studies in animals have demonstrated increased susceptibility to tuberculosis in association with transgenic expression of the soluble portion of tumor necrosis factor receptor 1 (TNFR1).<sup>35</sup> Although the numbers of patients who have been exposed to etanercept and infliximab are similar, only 9 cases of tuberculosis in patients treated with etanercept have been reported to the FDA, as compared with 70 cases in patients treated with infliximab. This difference may reflect the different ways in which the two agents neutralize TNF- $\alpha$ .<sup>25</sup> The proportion of patients treated with infliximab rather than etanercept is larger in Europe than in other countries (Table 1), and the majority of the reports are from Europe. These and other factors may also explain the difference in the number of reported cases of tuberculosis associated with the two agents.

Since there is underreporting with all passive sur-

veillance systems, the AERS reports probably represent only a subgroup of incident cases.<sup>36</sup> Nonetheless, the rate of reported cases in the United States among infliximab-treated patients with rheumatoid arthritis is substantially higher than the estimated background rate for patients with rheumatoid arthritis in the United States. In a randomized, double-blind, placebo-controlled trial of infliximab treatment in patients with rheumatoid arthritis in Europe, there were no cases of tuberculosis among the 88 patients who received placebo and methotrexate.<sup>14</sup> Among the 340 patients treated with infliximab and methotrexate, disseminated tuberculosis was diagnosed in 1 patient after a protracted illness; the patient was treated for tuberculosis but died. Adalimumab, an investigational antibody against TNF- $\alpha$  that is similar to infliximab, has been associated with tuberculosis in clinical trials involving patients with rheumatoid arthritis.<sup>37</sup> The association was seen with high doses of adalimumab but not with lower doses, suggesting that there is a dose-response effect. Taken together, these data suggest that the risk of tuberculosis is higher among infliximab-treated patients with rheumatoid arthritis than among patients with rheumatoid arthritis who do not receive this agent. Infliximab currently leads all other drugs and biologic products with respect to the number of cases of tuberculosis reported to the AERS. The association between the use of infliximab and reactivation tuberculosis is strong but not proven. The manufacturer of the drug has recognized the concern about this association, and the product's package insert now includes a warning about the risk of tuberculosis and the need to screen patients for tuberculosis before treatment with infliximab is initiated.

The pattern of tuberculosis observed after anti-TNF- $\alpha$  treatment may be due to the failure of granulomas to compartmentalize viable *M. tuberculosis* bacilli, but the underlying mechanism is unclear. TNF- $\alpha$  is an inflammatory cytokine that can induce a broad spectrum of biologic effects mediated by TNFR1 and TNFR2.<sup>38</sup> Signals from these receptors mediate apoptosis and the activation of nuclear factor- $\kappa$ B, which can influence the production of cytokines and the expression of adhesion molecules.<sup>39</sup> Mohan et al. noted that in a mouse model of latent tuberculosis, reactivation of disease followed the neutralization of TNF- $\alpha$  with TNF- $\alpha$  antibodies.<sup>7</sup> They also reported markedly increased infiltration of the lung with immune cells — an increase that was disproportionate to the bacillary load. This finding is consistent with the extensive infiltration in the lung specimen from our index patient, although acid-fast bacilli were not seen in the specimen. One mechanism by which TNF- $\alpha$  is thought to mediate a successful host response to mycobacteria is the orderly induction of macrophage apoptosis after bacillary infection.<sup>24,40</sup> Macrophage apoptosis is a prominent feature of tuberculosis-associated granulomas<sup>19,22</sup> (Fig. 2B) and may help maintain their integ-

ity. Yet apoptosis was rare in the pathological specimen from our index patient (Fig. 2D). There probably are many mechanisms that lead to apoptosis in tuberculosis, and infliximab may affect one or more of these mechanisms. Taken together, these observations suggest that an interruption of TNF- $\alpha$  activity may allow an aberrant immune response to a small number of tubercle bacilli. This abnormal response may have important pathologic effects.

Our findings have important clinical implications. Infliximab is an effective treatment for two debilitating diseases for which other treatments are frequently inadequate.<sup>10,11</sup> Physicians should be aware of the increased risk of reactivation of tuberculosis among patients who are receiving infliximab and other immunosuppressive agents and, in particular, of the unusual clinical manifestations of the disease. When active tuberculosis is suspected, treatment with infliximab should be stopped until the diagnosis has been ruled out or the infection has been treated with antituberculosis agents. Before treatment with infliximab is initiated, every effort should be made to determine whether the patient has latent tuberculosis infection. Since tuberculin tests may have false negative results in systemically ill or immunosuppressed patients, a detailed assessment of the risk of tuberculosis should be performed in every case. In our opinion, patients with latent infection should be given prophylactic treatment to prevent active disease before infliximab is administered. Physicians prescribing infliximab should advise patients to seek medical attention if they have symptoms suggestive of tuberculosis while taking the drug.

Supported by grants to Dr. Keane from the National Heart, Lung, and Blood Institute (HL-03964), the Massachusetts Thoracic Society, and the American Lung Association of Massachusetts.

We are indebted to Drs. Hardy Kornfeld, John Bernardo, Susan Ellenberg, Jay Siegel, and Robert Ball for their careful review of the manuscript and constructive comments; and to Dr. Manette Niu for her review of the early reports of tuberculosis and her review of the manuscript.

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