Mycobacterium fortuitum infection complicating infliximab therapy in rheumatoid arthritis

Sirs,

Tumor necrosis factor-α (TNF-α) antagonists have rapidly emerged as an invaluable class of antirheumatic agents in patients with chronic inflammatory diseases. The most frequent significant adverse events with these agents are infections, with intracellular slow growing agents like tuberculosis (TB) of special concern. We report the first case of granulomatous hepatitis due to *mycobacterium fortuitum* (MF) in a patient treated with infliximab.

A 73-year-old woman was admitted to the hospital because of persistently elevated liver enzymes. She had been treated for seronegative RA for 20 years. Three months earlier infliximab 3mg/kg had been added to the previous methotrexate (MTX) 15 mg/week. Her 11mm tuberculin skin test (TST) reaction was erroneously reported to the rheumatologist as negative. While initial liver enzymes were recorded as normal, routine blood studies at 2 months revealed elevated liver enzymes (Table I) and MTX was stopped. No improvement was noted on repeat studies after three weeks.

On admission her examination was remarkable only for chronic arthritis. Laboratory tests were normal except for C reactive protein concentration and liver enzymes (Table I).

On the fourth hospital day, her temperature rose to 38.70ºC accompanied by chills, with liver enzyme levels rising further (Table I). Amikacin was started empirically for treatment of a presumed hospital acquired superficial phlebitis in an immunosupressed patient. On the third day of antibiotic treatment, a liver biopsy was performed. Histological examination revealed florid granulomatous hepatitis with non necrotizing granulomas, with biopsy culture negative, but PCR positive for *mycobacterium fortuitum* (MF) with confirmation on repeat testing. Sputum was negative for Ziel Nielsen staining. A repeat TST was positive at 22 mm. The antibiotic treatment was changed to ciprofloxocin with liver enzymes improving, notably after three months (Table I). The patient felt well; ciprofloxocin was discontinued; treatment with MTX was resumed; and liver enzymes remained normal.

Clinical use of anti- TNF-α agents, particularly the antibodies, has been implicated in the reactivation of recent or remotely acquired tuberculosis infection (1-4), and an increase in nontuberculous mycobacterial (NTB) infection as well (5).

Table I. Serum liver enzymes and C reactive protein (CRP) in a patient with granulomatous hepatitis before and after treatment for *mycobacterium fortuitum.*

Blood chemical analysis	Normal range	Before admission	On admission	Fourth hospital day	Three weeks after treatment	Three months after treatment
AST	6-32 U/L	60	87	107	84	25
ALT	6-31 U/L	80	219	148	75	30
GGT	7-36 U/L	230	868	1830	530	34
Alkaline phosphate	35-110 U/L	150	186	337	170	92
CRP	0-6 mg/dl	27	38	89	22	4.5

NTB includes *mycobacterium avium complex* and rapidly growing *mycobacterium* (RGM): *fortuitum, chelonae* and *abscessus.* The most common of this group, MF, causes human infection primarily by direct inoculation, including primary skin and soft tissue infection, pulmonary disease and disseminated infection (6), as well as granulomatous hepatitis (7). The TST demonstrates induration of 10-14 mm or more for the majority of these patients (8). Unlike TB, MF infection typically responds well to a wide spectrum of antibiotics including imipinem, rifampicin, ciprofloxacin, doxycycline and amikacin, optimally for 6-12 months (9). The PCR was positive for MF, with TST borderline positive before infliximab and grossly abnormal during the clinical illness. In the present case, MF infection, similar to that described in TB, appeared after three infusions of infliximab. Liver culture was likely negative due to concurrent treatment for phlebitis with an antibiotic coincidentally also effective in eradicating MF. On a Medline search, no previous reported documentation of this RGM complication of anti-TNF treatment was found. Ongoing postmaketing surveillance of such serious adverse events to determine the true incidence rates, toward a reassessment of the overall risk-benefit of anti-TNF treatment is suggested (10).

N. BOULMAN, *MD*[1]
M. ROZENBAUM, *MD*[1]
G. SLOBODIN, *MD*[2]
I. ROSNER, *MD*[1]

[1]Department of Rheumatology, [2]Internal Medicine A, Bnai Zion Medical Center, Technion-Rappaport Faculty of Medicine, Haifa, Israel.

Address correspondence to: Dr. Nina Boulman, Department of Rheumatology, Bnai Zion Medical Center, 47 Golomb St., P.O.Box 4940, Haifa 31048, Israel
E-mail: rosneri@tx.technion.ac.il

References:

1. CRISCIONE LG, ST CLAIR EW: Tumor necrosis factor-alpha antagonists for the treatment of rheumatic diseases. *Curr Opin Rheumatol* 2002;14: 204-11.
2. STRAND V, KEYSTONE E: Anticytokine therapies in rheumatoid arthritis. 2004, www.uptodate.com
3. DINARELLO CA: Anti-cytokine therapeutics and infections. *Vaccine* 2003; 21 (Suppl. 2): S24-34.
4. GARDAM MA, KEYSTONE EC, MENZIES R *et al.*: Anti-tumor necrosis factor agents and tuberculosis risk: mechanisms of action and clinical management. *Lancet Infect Dis* 2003; 3: 148-55.
5. GRIFFTH DE, WALLACE RJ: Clinical manifestations of nontuberculosus mycobacterial infections in HIV-negative patients. 2004, www.uptodate.com
6. INGRAM CW, TANNER DC, DURACK DT, KERNODLE GW JR, COREY GR: Disseminated infection with rapidly growing mycobacteria. *Clin Infect Dis* 1993; 16: 463-71.
7. BRANNAN DP, DUBOIS RE, RAMIREZ MJ, RAVRY MJ, HARRISON EO: Cefoxin therapy for Mycobacterium fortuitum bacteremia with associated granulematous hepatitis. *South Med J* 1984; 77: 381-4.
8. BAHRMAND AR, MADANI H, SAMAR G *et al.*: Detection and identification of non-tuberculous mycobacterial infection in 6,427 tuberculosis suspected patients. *Scand J Infect Dis* 1996; 28: 275-8.
9. LEIBOWITZ MR, CURRIER JS: Overview of nontuberculous mycobacteria (excluding MAC) in HIV-infected patients.2004, www.uptodate.com
10. IMPERATO AK, BINGHAM CO 3RD, ABRAMSON SB: Overview of benefits/risk of biological agents. *Clin Exp Rheumatol* 2004; 22 (Suppl. 35): S108-14.