Dear Editor,

Therapy with tumor necrosis factor (TNF-α) antagonists (infliximab, etanercept and adalimumab) has been associated with an increased risk of reactivating granulomatous diseases and other intracellular bacterial infections, in which host defenses are particularly macrophage dependent. Several cases of *Listeria monocytogenes* infection have been reported in patients with rheumatic, dermatologic, and inflammatory bowel diseases (IBD) while receiving TNF-α antagonist (1). We describe a case of listeriosis in patients with IBD receiving tumor TNF-α antagonists, and review of previous reports recovered from PubMed database (2000 to 2008).

A 50 year-old woman with history of Crohn’s disease who was on azathioprine 150 mg p.o q.d, and mesalazine 500 mg p.o. b.i.d, presented to the Emergency Department with fever, weakness, headache, and malaise 3 weeks after her third course of treatment with infliximab 5 mg/kg intravenously (0, 2 and 6 weeks). On physical examination, the patient was febrile (38.5 ºC); neurologic, cardiorespiratory and abdominal examination was unrevealing. The white blood cell count was 7.48 x 10^3 /µL with a left shift in the differential, and the C-reactive protein, 108 mg/L. Chest-X-ray revealed no abnormalities. Blood and urinary culture were obtained. She was discharged six hours after admission on therapy with non-steroidal anti-inflammatory drugs without antibiotics. After an incubation period of 48 hours the blood culture yielded grampositive coccobacilli consistent with *Listeria* spp. At that time, the patient was still febrile and was admitted to hospital. She was started on ampicillin (2 g every 4 hours, i.v.) and gentamycin (80 mg every 8 hours i.v.). A lumbar puncture revealed a clear cerebrospinal fluid with a white blood cell count of 3 cells/mm3, total protein of 29.3 mg/dL and glucose of 47 mg/dL. The isolate was identified as *L. monocytogenes* that was sensitive to ampicillin. The clinical course was uneventful with full clinical recovery. She completed an intravenous antibiotic course for 10 days followed by oral amoxicillin (3 g daily) for 10 days more. Two months after the hospitalization, infliximab was restarted with no relapses during a 10-month follow-up.

In 2000, the first case of listeriosis in a patient with IBD receiving infliximab was reported (2). After that report, several cases have been described in the medical literature (1-11). There is a relevant report of a large case series by Slifman et at (2), that described 15 patients with listeriosis associated with the use of infliximab or etanercept coming from the Adverse Event Reporting System from 1998 through December 2001. A total of 13 cases of *Listeria* infections in patients with IBD were recovered from the literature (1-11). The summary of these cases and the case reported here is shown in table 1. The mean age in patients with IBD was 43.6 year (standard deviation: 15.5). One (9.1%) had comorbid concomitant diseases. All of cases occurred in patients using infliximab. All of 14 cases were receiving other immunosuppressive therapy (prednisone [n=14], azathioprine [n=7], and 6-mercaptopurine [n=4]) in addition to TNF-α antagonists. The mean of delay from starting therapy with TNF-α antagonists to diagnosis of listeriosis was 6.3 weeks (standard deviation: 11.7). The mean number of doses of infliximab was 2.5 (standard deviation: 2.8). The majority of listeriosis in patients with IBD suffered central nervous system infections and bacteremia [9 cases (64.5%)]. No patients suffered septic arthritis. The mortality rate in patients with IBD was 7.1%.

The mechanisms whereby listeriosis may develop in patients receiving TNF-alpha therapy have not been clearly established (1). TNF-alpha plays an important role in defense against intracellular organisms such as *Listeria* spp. TNF-α promotes macrophage recruitment to the area and stimulates the produc-
tion of nitric oxide necessary for microbial killing (1,11). Based on these observations, it is possible that the use of TNF-α antagonists may counteract the effect of endogenous TNF-α and promote the development of listeriosis in patients on periodical treatment with these drugs. * L. monocytogenes DNA has been detected in the intestine of both patients with IBD and in control patients without IBD (2,11). The ingestion of processed meat serves as a potential source of the organisms. Mucosal damage in patients with IBD harboring chronically Listeria spp. may make them more prone to develop listeriosis after treatment with infliximab. The mucosal damage of these patients may facilitate the invasion of the bacteria from gut to bloodstream.

In conclusion, several cases of listeriosis have already been reported in patients with IBD treated with TNF-α antagonists. Those patients may prone to develop this infection after few doses of anti-tumor necrosis factor therapy. The main clinical presentation is sepsis and meningitis.

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References


