**Leptospira interrogans icterohaemorrhagiae** in a Patient with Crohn’s Disease

**To the Editor:**

Leptospirosis is an acute water-borne anthro-po-zoonotic infection of worldwide significance caused by *Leptospira*. *Leptospira*, which belongs to the order *Spirochaetaceae*, is comprised of 2 distinct species. Within each species there are a number of serologically different serovars, arranged in related serogroups. *Leptospira* has 23 serogroups and more than 200 serovars. *Leptospira interrogans* var. *icterohaemorrhagiae* and *L. interrogans* var. *Hebdomadis* serovar *hardjo* are commonly reported.

Leptospirosis has spread from its traditional rural base to become the cause of epidemics in poor urban communities and poor sanitation environments in developing countries. Various factors influencing the animal activity, suitability of the environment for the survival of the organism, and behavioral and occupational habits of human beings can be the determinants of incidence and prevalence of the disease. Traditionally, water and sewage workers have been among those most frequently infected, but with improved healthcare awareness this group has been overtaken by farm workers and a growing group of people engaged in aquatic sports.

Symptoms of leptospiral infection vary in severity from a mild flu-like illness to symptoms resulting from severe renal, hepatic, or meningeal involvement. Leptospirosis generally presents as two separate clinical syndromes: the hepato-renal form and the pulmonary form. Moreover, the overall disease burden is underestimated, since leptospirosis is a significant cause of undifferentiated fever and frequently not recognized. Mortality remains significant, related both to delays in diagnosis due to lack of infrastructure and adequate clinical suspicion, and to other poorly understood reasons that may include inherent pathogenicity of some leptospiral strains or genetically determined host immunopathological responses. Mortality from severe disease forms, Weil’s disease and severe pulmonary hemorrhage syndrome, is high even when optimal treatment is provided.

A 54-year-old male diagnosed with Crohn’s disease (CD) was admitted to the Emergency Department because of fever and jaundice for the last 3 days. Except for ileal CD, the patient’s personal history was unremarkable. For 1 year the patient was on maintenance infliximab therapy and achieved long-term remission with good quality of life, allowing his hobby of hunting rabbits. One week before this admission the patient received maintenance infliximab and then he went hunting in a forest. Two days later he developed fever, myalgias, weakness, and jaundice.

On admission, physical examination revealed fever and jaundice without signs of abdominal tenderness. Laboratory tests showed deterioration, with peripheral blood platelets 15,000, total bilirubin 11 mg/dl (direct bilirubin 8 mg/dl), creatinine 6.5 mg/dl, and a 5-fold increase in transaminases. Hepatitis testing showed that the patient was vaccinated for hepatitis B and no abnormal hepatitis A, C, or E virus titers were found. Radiology and abdominal ultrasound were normal.

The patient was started on immediately empiric treatment with ceftriaxone 2 g and repeated blood and urine cultures were performed. On the second day of hospitalization the diagnosis of *Leptospira interrogans* infection was made and patient was transferred to the Department of Nephrology, as his creatinine was further deteriorated. On the fifth day of hospitalization the patient showed signs of clinical and laboratory improvement without needing dialysis and after 2 weeks of hospitalization the patient was discharged in very good condition.

In this patient the diagnosis of leptospirosis was very probable based on symptoms and laboratory findings as well as a history of hunting. In the same panel uremic hemolytic syndrome and Handaan virus could also be included.

*Leptospira interrogans* can be cultured using dark-ground microscopy from blood and cerebospinal fluid during the first week of leptospirosis and from urine thereafter. Since the isolation rate of *Leptospira* from clinical specimens is low due to prior indiscriminate use of antibiotics, serological techniques remain the cornerstone of diagnosis. In clinical practice, seroconversion can be detected by IgM-specific dot enzyme-linked immunosorbent assay (ELISA) techniques, a technique also used in the patient herein. The completion of the genome sequence of *Leptospira interrogans* and other continuing leptospiral genome sequencing projects promise to guide future work on the disease. No vaccine is available and prevention is largely dependent on sanitation measures that may be difficult to implement, especially in developing countries.

Studies of in vitro sensitivity indicate that *Leptospira* organisms are sensitive to most antibiotics. The mainstays of treatment are still tetracyclines and beta-lactam/cephalosporins. Mild symptoms respond to oral penicillin, erythromycin, or tetracyclines, while more serious illness requires intravenous penicillin and supportive nursing. Doxycycline has been shown to confer a beneficial effect in reducing the clinical illness and mortality during outbreaks. In this patient ceftriaxone was administered empirically before
diagnosis and was continued with success afterwards. In fact, ceftriaxone has been proven to be highly effective in laboratory studies and for clinical treatment.4

In this patient case the role of infliximab administration in acute leptospirosis is very questionable. The timing of infliximab administration was very close to the onset of this rare infection, but we believe that patient environmental exposure during hunting remains the primary etiologic factor for his acute illness. Furthermore, infliximab regular administration was continued in this patient after overcoming the episode of leptospirosis.

Tumor necrosis factor-alpha (TNF-α) is a proinflammatory cytokine involved in a wide range of important physiologic processes. This cytokine has a pathologic role in some diseases and TNF-α antagonists are effective in treating inflammatory conditions.5,6 Given the putative role of TNF-α in host defense against tuberculosis and other infections, the risk of infections and cancers with TNF-α antagonists was always a concern.7,8 In fact, infections associated with TNF-α-antagonist therapy have been widely reported. Infliximab, etanercept, and adalimumab may be associated with an increased risk of tuberculosis. Histoplasmosis, listeriosis, aspergillosis, coccidioidomycosis, and candidiasis have been associated with TNF-α antagonists, but the causative relationship is not clear. Potential recipients of these drugs should be rigorously screened with skin testing, detailed questioning about recent travel and potential tuberculosis exposure, and assessment for symptoms to minimize their risk of frequent or rare infections. To conclude, this is the first report of leptospirosis in a patient with CD also receiving infliximab. Patients receiving any kind of immunomodulator or anti-TNF-α therapy should always be advised to take care when exposing themselves to unpredictable environmental factors. Modifying outdoor hobbies in such groups of patients may be a possibility, but when advising we should always take into account the quality of their lives.

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REFERENCES