ANNALS OF GASTROENTEROLOGY 2010, 23(3):159-161

Editorial

Listeria monocytogenes infection in patients with Inflammatory Bowel Disease: Is there an increased risk with immunomodulators or biologic agents?

D. Christodoulou, E.V. Tsianos

Listeria monocytogenes is generally thought of as a foodborne pathogen that causes bacteremia and meningoencephalitis in individuals with impaired cell-mediated immunity, including neonates, pregnant women, elderly persons and immunosupressed recipients of transplants.[1,2] Although antecedent diarrhea has been reported in cases of invasive listeriosis (i.e. a case involving the presence of *L. monocytogenes* in a normally sterile site), it was only recently that *L. monocytogenes* was established as a cause of acute, self limited, febrile gastroenteritis in healthy persons.[3,4] At least 7 outbreaks of foodborne gastroenteritis for which *L. monocytogenes* was the most likely etiology have been described. The most commonly reported symptoms in those cases were fever, diarrhea, arthromyalgia and headache. Listeriosis can be manifested as a systemic illness associated with bacteremia, sepsis and central nervous system involvement including meningitis and encephalitis.[5,6]

Infections caused by *L. monocytogenes* complicating infliximab treatment for CD were first described in 2000.[7] Eight subsequent cases were reported in the literature in the next five years and six of those patients were also receiving immunomodulators (azathioprine or 6-mercaptopurine).[8] A review of the United States Food and Drug Administration Adverse Report Event Reporting Program produced three CD patients on infliximab who developed listeria septicemia and/or meningitis, one of whom died.[9] All patients were receiving concurrent immunosuppressive drugs, including a 17-year old girl reported by Kamath et al.[10] Meningitis caused by *L. monocytogenes* has also been reported in other patients treated with infliximab or adalimumab.[11-13] As noted by some authors, the most serious infections after anti-TNFα treatment usually occur after three or fewer infusions and most of the patients with inflammatory bowel disease were also concomitantly taking corticosteroids and azathioprine or 6-mercaptopurine.[14] Currently, there are no data on the incidence of listeriosis in Crohn's disease. A comparison of the rate of *L. monocytogenes* infection between patients who received infliximab versus those who did not is therefore impossible because population data are lacking. The extent to which other immunomodulating drugs influence susceptibility to serious infections in patients with infliximab is not clear. In a study, Colombel et al used a Cochrane-Mantel-Haenszel analysis to demonstrate that the use of combination treatment consisisting of corticosteroids and azathioprine, 6-mercaptopurine or methotrexate may increase the risk significantly.[15]

In contrast with Crohn's disease, there have been twice as many cases of rheumatoid arthritis reported in which anti-TNFα treatment was complicated by serious *Listeria* infections, including sepsis, meningitis and death.[9,13,14,16] Data from the United States indeed suggest that the rate of *L. monocytogenes infection* in infliximab-treated rheumatoid arthritis patients (5 of 82,000) may be higher than in Crohn's disease patients (two of 104,500) who received this drug.[9] This may be related to the greater use of methotrexate in rheumatoid arthritis, the different dose or dosing schedule of infliximab, or the higher median age of patients with rheumatoid disease. Infliximab-linked listeria infections have also been reported in patients with

1st Division of Internal Medicine, Hepato-Gastroenterology Unit, Medical School and University of Ioannina, Greece

Author for correspondence:

D. Christodoulou, MD, Assistant Professor of Gastroenterology, 1st Division of Internal Medicine, Medical School, University of Ioannina- Greece, University Campus, 45110, Ioannina, Greece, Phone: +3026510 99617, Fax: +30 26510 07883, e-mail: dchristo@uoi.gr

ulcerative colitis, psoriatic arthritis and juvenile rheumatoid arthritis.[9,17]

In the current issue of Annals of Gastroenterology, Triantafillidis et al,[18] reported a case of *Listeria* meningitis in an immunocompromised patient with ulcerative colitis. The patient was on long-term treatment with corticosteroids and azathioprine, but responded favorably to specific treatment with a combination of antibiotics for *Listeria.* The authors stressed that listeriosis generally occurs in patients under immunosuppressive treatment and in patients receiving monoclonal antibodies against TNF-α. Their patient developed *Listeria* meningitis after an exacerbation of ulcerative colitis, which required an intensified treatment with corticosteroids and azathioprine. Prompt and repeated examination of the cerebrospinal fluid immediately after the development of central nervous system symptoms led to the diagnosis of listeriosis and to successful treatment with a combination of ampicilline and gentamycin. Finally the patient was referred for colectomy to avoid the risks of long-term steroids and immunosuppressive administration.

The authors stressed that very few cases of *L. monocytogenes* meningitis have been described in patients with ulcerative colitis under immunosuppressive treatment, while such an infection is more frequent in patients receiving biologic agents.[19] Patients under immunosuppressive treatment should probably avoid consumption of soft cheeses and unpasteurized dairy products and must always reheat processed meats until steaming, but the overall risk of *Listeria* infection is very small. Interestingly the presence of lymphocytosis in the cerebrospinal fluid does not exclude *Listeria* meningitis. Finally, it is generally thought that *L. monocytogenes* is not directly related to the pathogenesis or exacerbation of ulcerative colitis or Crohn's disease.

In the same issue, Katsanos et al,[20] reported in a letter to the Editor a case of *L. monocytogenes* infection in a patient with ulcerative colitis, just two days after the first dose of infliximab. The patient was also on methylprednizolone treatment and in the past he had also received azathioprine, so he had probably been already immunocompromised. It is also possible that he was already a carrier of *L. monocytogenes*, so the infliximab infusion just led to the development of bacteremia and clinical infection. The patient had a favorable outcome with the combination of ampicillin and gentamycin and should be evaluated with caution in the future for the reinstitution of infliximab treatment.

Apart from its proinflammatory role, TNF-α also plays an important role in the defense against microbial infections. The interaction between *Listeria* infection and the host response is complex,[21] but there is good evidence suggesting that TNF-α plays an important role in host defense against *L. monocytogens.* Recent studies have shown that TNF-α deficient mice are highly susceptible to *L. monocytogens.* The presence of this cytokine and its type I receptor, p55, seems to be critical for resistance against primary infection by this intracellular pathogen.[22]

It is therefore evident that the immunosuppressive properties of corticosteroids and azathioprine and the anti-TNFα effects of biologic agents, are on one hand of great benefit to patients with inflammatory bowel disease, but may, on the other hand, rarely, predispose them to serious infections, such as listerosis. The occurrence of infection shortly after the initiation of infliximab could be consistent with reactivation of latent infection. Therefore, recommendations to avoid foods such as soft cheeses and unpasteurized dairy products and to reheat (until steaming) processed meats such as hot dogs seem very reasonable in patients starting immunosuppressives or infliximab therapy. As shown by the articles presented in this issue of Annals of Gastroenterology, this risk is present in patients with ulcerative colitis and not only in Crohn's disease patients. Clinicians should be aware of this complication after infliximab infusions or immunosuppression and should consider aggressive investigation and empirical antibiotic treatment in patients with new onset central nervous system symptoms.

REFERENCES

1. Chiba M, Fukushima T, Koganei K, Nakamura N, Masamune O. Listeria monocytogenes in the colon in a case of fulminant ulcerative colitis. Scand J Gastroenterol 1998; 3:778-782.
2. Chiba M, Fukushima T, Inoue S, Horie Y, Iizuka M, Masamune O. Listeria monocytogenes in Crohn's disease. Scand J Gastroenterol 1998; 33:430-434.
3. Schlech WF. An Animal-Model of Foodborne Listeria-Monocytogenes Virulence - Effect of Alterations in Local and Systemic Immunity on Invasive Infection. Clinical and Investigative Medicine-Medecine Clinique et Experimentale 1993; 16:219-225.
4. Schlech WF, Schlech WF, Haldane H, et al. Does sporadic Listeria gastroenteritis exist? A 2-year population-based survey in Nova Scotia, Canada. Clinical Infectious Diseases 2005; 41:778-784.
5. Wiesmayr S, Tabarelli W, Stelzmueller I et al. Listeria meningitis in transplant recipients. Wiener Klinische Wochenschrift 2005; 117:229-233.
6. Ye S, Yang CD. Central nervous system infections in the systemic vasculitides. Current Opinion in Neurology 2008; 21:342-346.

7. Morreli J, Wilson FA. Does administration of infliximab increase susceptibility to listeriosis. Am J Gastroenterol 2000; 95:841-842.
8. Williams G, Khan AA, Schweiger F. Listeria meningitis complicating infliximab treatment for Crohn's disease. Can J Infect Dis Med Microbiol 2005; 16:289-292.
9. Slifman NR, Gershon SK, Lee JH, Edwards ET, Braun MM. Listeria monocytogenes infection as a complication of treatment with tumor necrosis factor alpha-neutralizing agents. Arthritis and Rheumatism 2003; 48:319-324.
10. Kamath BM, Mamula P, Baldassano RN, Markowitz JE. Listeria meningitis after treatment with infliximab. Journal of Pediatric Gastroenterology and Nutrition 2002; 34:410-412.
11. Ghazi L, Choudhary C, Katz LC, Squires K, Kastenberg D. Listeria monocytogenes (LM) bacteremia after infliximab for Crohn's disease (CD). Am J Gastroenterol 2006; 101: S392.
12. Gil C, Legido J, Cuenca C et al. Meningitis due to Listeria monocytogenes during adalimumab therapy. Gastroenterologia y Hepatologia 2009; 32:587-588.
13. Tweezer-Zaks N, Shiloach E, Spivak A, Rapoport M, Novis B, Langevitz P. Listeria monocytogenes sepsis in patients treated with anti-tumor necrosis factor-alpha. Israel Medical Association Journal 2003; 5:829-830.
14. Bowie VL, Snella KA, Gopalachar AS, Bharadwaj P. Listeria meningitis associated with infliximab. Annals of Pharmacotherapy 2004; 38:58-61.
15. Colombel JF, Loftus EVJr, Tremaine WJ, et al. The safety profile of infliximab in patients with Crohn's disease: The Mayo clinic experience in 500 patients. Gastroenterol 2004; 126:19-31.
16. Gluck T, Linde HJ, Scholmerich J, Muller-Ladner U, Fiehn C, Bohland P. Anti-tumor necrosis factor therapy and Listeria monocytogenes infection: report of two cases. Arthritis and Rheumatism 2002; 46:2255-2257.
17. Aparicio AG, Munoz-Fernandez S, Bonilla G, Miralles A, Cerdeno V, Martin-Mola E. Report of an additional case of anti-tumor necrosis factor therapy and Listeria monocytogenes infection: comment on the letter by Gluck et al. Arthritis and Rheumatism 2003; 48:1764-1765.
18. Triantafillidis J, Sklavaina M, Panteris V, Georgopoulos F, Merikas E. Listeria meningitis in an immunocompromised patient with ulcerative colitis: a report of a case and review of the literature. Annals of Gastroenterology 2010; 23:205-208.
19. Quispel R, van der Worp HB, Pruissen M, Schipper ME, Oldenburg B. Fatal aseptic meningoencephalitis following infliximab treatment for ulcerative colitis. Gut 2006; 55:1056.
20. Katsanos K, Kostapanos M, Zois C, Vagias I, et al. Listeria monocytogenes infection two days after infliximab initiation in a patient with ulcerative colitis. Annals of Gastroenterology 2010; 23:209-210
21. Edelson BT, Unanue ER. Immunity to Listeria infection. Curr Opin Immunol 2000; 12:425-431.
22. White DW, Badovinac VP, Fan X, Harty JT. Adaptive immunity against *Listeria monocytogenes* in the abscence of type I tumor necrosis factor receptor p55. Infection and Immunity 2000; 68:4470-4476.