

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

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*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 immunosuppressed recipients of transplants.<sup>1,2</sup> 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.<sup>3,4</sup> 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, arthralgia and headache. Listeriosis can be manifested as a systemic illness associated with bacteremia, sepsis and central nervous system involvement including meningitis and encephalitis.<sup>5,6</sup>

Infections caused by *L. monocytogenes* complicating infliximab treatment for CD were first described in 2000.<sup>7</sup> 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).<sup>8</sup> 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.<sup>9</sup> All patients were receiving concurrent immunosuppressive drugs, including a 17-year old girl reported by Kamath et al.<sup>10</sup> Meningitis caused by *L. monocytogenes* has also been reported in other patients treated with infliximab or adalimumab.<sup>11-13</sup> As noted by some authors, the most serious infections after anti-TNF $\alpha$  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.<sup>14</sup> 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 consisting of corticosteroids and azathioprine, 6-mercaptopurine or methotrexate may increase the risk significantly.<sup>15</sup>

In contrast with Crohn's disease, there have been twice as many cases of rheumatoid arthritis reported in which anti-TNF $\alpha$  treatment was complicated by serious *Listeria* infections, including sepsis, meningitis and death.<sup>9,13,14,16</sup> 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.<sup>9</sup> 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

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ulcerative colitis, psoriatic arthritis and juvenile rheumatoid arthritis.<sup>9,17</sup>

In the current issue of *Annals of Gastroenterology*, Triantafyllidis et al,<sup>18</sup> 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- $\alpha$ . 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 ampicillin 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.<sup>19</sup> 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,<sup>20</sup> 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 methylprednisolone 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 reinstatement of infliximab treatment.

Apart from its proinflammatory role, TNF- $\alpha$  also plays an important role in the defense against microbial infec-

tions. The interaction between *Listeria* infection and the host response is complex,<sup>21</sup> but there is good evidence suggesting that TNF- $\alpha$  plays an important role in host defense against *L. monocytogenes*. Recent studies have shown that TNF- $\alpha$  deficient mice are highly susceptible to *L. monocytogenes*. The presence of this cytokine and its type I receptor, p55, seems to be critical for resistance against primary infection by this intracellular pathogen.<sup>22</sup>

It is therefore evident that the immunosuppressive properties of corticosteroids and azathioprine and the anti-TNF $\alpha$  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 listeriosis. 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.

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