

Listeria meningitis complicating infliximab treatment for Crohn's disease

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Infliximab, a monoclonal antibody directed against tumour necrosis factor-alpha, is an effective therapy for Crohn's disease. Though uncommon, serious opportunistic infections, including reactivation of tuberculosis, have occurred in patients after infliximab administration.

Meningitis caused by *Listeria monocytogenes* developed in a 37-year-old man six days after the second infusion of infliximab. The patient, who also was treated with azathioprine and corticosteroids, had an uneventful recovery after a course of antibiotics. Several other recent reports have implicated infliximab therapy in the development of severe *Listeria* infections, particularly meningitis and sepsis. With the increasing use of tumour necrosis factor-alpha-neutralizing agents, clinicians should be aware of the risk of opportunistic infections caused by *L monocytogenes* in patients with Crohn's disease following infliximab treatment.

Key Words: *Crohn's disease; Infliximab; Listeria meningitis*

Infliximab, a human/murine chimeric monoclonal antibody directed against tumour necrosis factor-alpha (TNF- α), is a new and effective therapy for active Crohn's disease (CD), and chronic refractory and fistulizing disease (1-3).

Early studies reported low rates of adverse effects in patients treated with infliximab for CD (4). However, recent studies point toward infrequent but potentially serious events, including opportunistic infections and sepsis (3,5,6).

Listeria monocytogenes, a Gram-positive intracellular bacillus, can be isolated from well water, sewage, and the intestinal tract of humans and animals. This organism can cause sporadic or epidemic infection, and can be found in the feces of 1% to 5% of asymptomatic, healthy adults. Transmission occurs via contaminated food such as unpasteurized milk, soft cheeses, cole slaw, undercooked meats and raw vegetables (7). Human disease generally occurs at the extremes of life (younger than two months or older than 60 years of age) or in the setting of pregnancy or immunosuppression, and manifests

Traitement de la maladie de Crohn par infliximab compliqué d'une méningite à *Listeria*

L'infliximab, un anticorps monoclonal dirigé contre le facteur de nécrose tumorale alpha, est un traitement efficace de la maladie de Crohn. Bien que rares, des infections opportunistes, dont la réactivation de la tuberculose, sont survenues chez certains patients à la suite d'un traitement par infliximab.

Ainsi, une méningite à *Listeria monocytogenes* s'est développée chez un homme de 37 ans, six jours après sa deuxième perfusion d'infliximab. Le patient, qui prenait également de l'azathioprine et des corticostéroïdes, s'est rétabli sans complications après une antibiothérapie. Plusieurs autres rapports ont récemment mentionné le rôle de l'infliximab dans le développement de graves infections à *Listeria*, surtout la méningite et la septicémie. Compte tenu de l'emploi de plus en plus répandu d'agents neutralisant le facteur de nécrose tumorale alpha, les médecins doivent être au courant des risques d'infections opportunistes à *L monocytogenes* chez les patients atteints de maladie de Crohn après un traitement par infliximab.

itself as a systemic illness associated with bacteremia, sepsis, meningitis and other systemic complications (8). Case mortality has been estimated to be 27%, and many patients with central nervous system involvement are left with neurological sequelae (8).

We describe a patient with severe Crohn's colitis who developed listeria meningitis six days after his second infusion of infliximab. A review of the literature suggests that this particular complication after anti-TNF- α administration may be seen increasingly in clinical practice with the rising use of this medication.

CASE PRESENTATION

A 37-year-old man presented with a two-week history of nausea, vomiting, abdominal cramps and diarrhea associated with some blood. He reported weight loss (4 kg), fever and chills over the preceding 10 days. On examination, he was dehydrated, hypotensive and had diffuse abdominal tenderness.

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TABLE 1
Listeria infections in Crohn's disease patients treated with infliximab

Age/sex	Doses	Concomitant drugs	Type of infection	Outcome	Authors
67/M	3	Prednisone, azathioprine, 5-ASA	Blood	Recovered	Morelli et al (17)
17/F	1	Methylprednisolone, 6-MP, 5-ASA	Blood, meningitis	Recovered	Kamath et al (19)
64/F	1	Prednisone, 6-MP, glyburide	Blood	Recovered	Slifman et al (18)
39/F	3	Prednisone, 6-MP, 5-ASA	Blood, meningitis	Recovered, paralysis of one eye	Slifman et al (18)
20/M	1	Methylprednisolone, azathioprine, metronidazole, 5-ASA	Meningitis	Death	Slifman et al (18)
48/M	1	None	Blood, splenic abscess	Recovered	Tweezer-Zaks et al (21)
41/F	1	Prednisone, azathioprine	Meningitis	Recovered	Joosten et al (20)
Not known	Not known	Not known	Meningitis	Recovered	Ljung et al (6)

5-ASA 5-Aminosalicylic acid; 6-MP 6-Mercaptopurine; F Female; M Male

Investigations revealed the presence of *Bacteroides fragilis* bacteremia, but stool testing for bacterial pathogens, *Clostridium difficile* toxins and parasites was negative. Flexible sigmoidoscopy showed severe colitis with deep ulcerations in the sigmoid colon consistent with CD. He improved with intravenous fluids, broad-spectrum antibiotics and corticosteroids, and was discharged after three weeks in hospital.

One week later, he redeveloped diarrhea, cramps and blood in the stool, which required rehospitalization. Intravenous methylprednisolone, azathioprine and 5-aminosalicylic acid (5-ASA) were administered. With no improvement after three days, 5 mg/kg of infliximab was infused, which resulted in remarkable improvement of his symptoms and early discharge.

The patient received a second infusion of infliximab (5 mg/kg) one month after the first infusion as an outpatient. At that time, he also was on a daily dose of prednisone (35 mg), 5-ASA (4 g) and azathioprine (1.8 mg/kg). Clinically, the patient felt improved and had two to three semiformal bowel movements per day.

Six days later, he presented with fever, tachycardia, diaphoresis and confusion. His temperature was 40°C. There were no signs of meningeal irritation and no focal neurological findings. Laboratory data showed a white blood cell count of $14.5 \times 10^9/L$, a hemoglobin level of 125 g/L, a platelet count of $501,000 \times 10^9/L$ and an erythrocyte sedimentation rate of 84 mm/h. Cranial computerized tomography was normal. Lumbar puncture yielded cloudy cerebrospinal fluid (CSF) with a white blood cell count of $3290 \times 10^6/L$, with 88% being polymorphonuclear neutrophils (normal range 0 to $5 \times 10^6/L$). The CSF glucose level was decreased at 1.5 mmol/L (normal

range 2.8 mmol/L to 4.4 mmol/L) and total CSF protein concentration was increased at 1.50 g/L (normal range 0.15 g/L to 0.45 g/L). Microscopy showed Gram-positive bacilli. CSF and blood cultures identified the organism as *L monocytogenes*.

The patient was initially treated with intravenous ampicillin and gentamicin, and was then switched to intravenous ampicillin and trimethoprim-sulfamethoxazole, thereby completing a total of three weeks of antibiotic treatment. He recovered completely without any neurological sequelae.

His inflammatory bowel disease is currently in remission on 4 g of 5-ASA and 2.5 mg/kg/day of azathioprine.

DISCUSSION

Adverse effects of infliximab therapy include infusion reactions, serum sickness-like disease and the development of autoantibodies (particularly antinuclear antibodies); these effects are rarely complicated by a lupus-like syndrome (3).

However, there has been increasing concern about infectious complications following infliximab infusions. Recent data from A Crohn's disease Clinical trial Evaluating infliximab in a New long term Treatment regimen (ACCENT I) (3) and the Mayo Clinic (5) in Rochester, Minnesota, USA, have shown that 32% and 8.2% of patients developed infections after infliximab infusion, respectively. Serious infections, including sepsis, occurred in approximately 4% of patients treated in both studies (3,5), and there seemed to be no correlation between the number of infusions and the rate of infectious events (3,5,9). When it was recognized that reactivation of tuberculosis could develop soon after treatment with infliximab, screening for latent tuberculous infection or active disease before therapy was advised (9). Several other opportunistic infections have been reported following infliximab infusion, including pneumocystosis, pulmonary aspergillosis, histoplasmosis, severe candida infections, coccidioidomycosis, cryptococcosis, cytomegalovirus, varicella-zoster virus and Epstein-Barr virus infections (5,9-16).

Infections caused by *L monocytogenes* complicating infliximab treatment for CD were first described in 2000 (17). The eight cases reported in the literature to date are summarized in Table 1. A review of the United States Food and Drug Administration's Adverse Event Reporting Program produced three CD patients on infliximab who developed listeria septicemia and/or meningitis (18), one of whom died. All patients were receiving concurrent immunosuppressive drugs, including a 17-year-old girl reported by Kamath et al (19). Two additional cases were mentioned in an addendum to the report by Slifman et al (18), but no further detail was provided. In addition, meningitis caused by *L monocytogenes* has recently been reported in three patients with CD treated with infliximab (6,20,21), and the present patient constitutes the ninth reported case.

Listeria meningitis occurred in the present patient after the second infusion of infliximab while on azathioprine and corticosteroids. He received the drug four weeks instead of two weeks after the first infusion due to a scheduling error. As noted by others, the most serious infections after infliximab treatment occur after three or fewer infusions (5,9,18), and almost all of the reported patients with inflammatory bowel disease were also concomitantly taking corticosteroids and azathioprine or 6-mercaptopurine (17-20,22). Currently, there are no data on the incidence rate of listeriosis in CD. A comparison of the rate of *L monocytogenes* infection between patients who

received infliximab versus those who did not is therefore impossible because population-based data are lacking. The extent to which other immunomodulating drugs influence susceptibility to serious infections in patients on infliximab is not clear. In a recent study, Colombel et al (5) used a Cochran-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.

In contrast with CD, there have been twice as many cases of rheumatoid arthritis reported in which anti-TNF- α treatment was complicated by serious listeria infections, including sepsis, meningitis and death (18,21-23). Data from the United States indeed suggest that the rate of *L monocytogenes* infection in infliximab-treated rheumatoid patients (five of 82,000) may be higher than in CD patients (two of 104,500) who received this drug (18). 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 ulcerative colitis, psoriatic arthritis and juvenile rheumatoid arthritis (18,24).

Infliximab reduces mucosal inflammation by several mechanisms of action (25). It binds and clears soluble TNF- α , thereby neutralizing its proinflammatory effects. It also binds to cell-bound TNF- α on macrophages and T cells, which interferes with direct cell-to-cell interactions and facilitates their destruction. Furthermore, in active CD, infliximab induces apoptosis of peripheral blood monocytes and leads to an increase in the number of apoptotic T lymphocytes in the lamina propria (25).

TNF- α plays a pivotal role in the pathogenesis of CD, and a marked increase of this cytokine is found in the intestinal mucosa of patients (26,27).

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 (28), but there is good evidence suggesting that TNF- α plays an important role in host defense against *L monocytogenes*. Recent studies, for example, have shown that TNF- α -deficient mice were highly susceptible to *L monocytogenes* infection (29,30). The presence of this cytokine and its type I receptor, p55, seems to be critical for resistance against primary infection by this intracellular pathogen (31).

It is therefore evident that the anti-TNF- α effects of infliximab are, on one hand, of great benefit to patients with CD but may, on the other hand, predispose them to serious infections such as listeriosis. This risk was addressed by the drug manufacturer by issuing a warning regarding the possible increased occurrence of opportunistic infections, including listeria (16). It is not clear whether infection originates from ingestion of contaminated food or from chronic fecal carriage in these immunocompromised patients. Indeed, the occurrence of infection shortly after the initiation of therapy with infliximab could be consistent with reactivation of latent infection (32). 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 infliximab therapy (19,23). Clinicians should be aware of this complication after infliximab infusions and should consider aggressive investigation and empirical antibiotic treatment in patients with new-onset central nervous system symptoms.

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