

## Case Report

# Listeria meningitis in an immunocompromised patient with ulcerative colitis: Report of a case and review of the literature

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## SUMMARY

This is the case of a patient with total ulcerative colitis on long-term treatment with corticosteroids and azathioprine and development of *Listeria meningitis*. Diagnosis was confirmed with cerebrospinal fluid culture. The patient responded favorably to specific treatment with a combination of antibiotics. It was not clear whether infection originated from ingestion of contaminated food or from chronic faecal carriage. Clinicians should be aware of the possibility of development of *Listeria Monocytogenes meningitis* in patients with ulcerative colitis being on long-term treatment with immunosuppressives and corticosteroids. Clinicians should also consider aggressive investigation and empirical antibiotic treatment in patients with new-onset symptoms originating from the central nervous system.

**Key Words:** *Listeria* infection, meningitis, immunosuppression, inflammatory bowel disease, Crohn's disease, ulcerative colitis.

cooked meats and raw vegetables.<sup>1,2</sup> *Listeria* can be isolated from well water, sewage, and the intestinal tract, and can be found in the faeces in up to 5% of healthy adults. The disease may be manifested as a systemic illness associated with bacteraemia, sepsis, and central nervous system involvement including meningitis.<sup>3,4</sup>

Human disease generally occurs in patients under immunosuppressive treatment and corticosteroids including patients with CD and UC.<sup>5</sup> During recent years a rapidly increasing number of cases of *Listeria meningitis* in patients with IBD receiving monoclonal antibodies against TNF- $\alpha$  (infliximab, adalimumab) were described.<sup>6</sup> However, descriptions of cases with meningitis due to *Listeria Monocytogenes* in patients with UC under treatment with immunosuppressives and corticosteroids are scarce.<sup>2</sup>

We report a case of a patient with UC who developed *Listeria meningitis* while being on azathioprine and corticosteroids. This particular combination of drugs seems to predispose to the appearance of this complication in patients with UC and the physicians must be aware of this possibility in order to early diagnose and treat the patient.

## INTRODUCTION

*Listeria monocytogenes* is a Gram-positive intracellular microorganism causing epidemic or sporadic infection. Transmission can be possible by mouth via contaminated food including unpasteurized milk, soft cheeses, under-

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## CASE REPORT

A woman, 64 years old, was admitted to the hospital because of fever, mental confusion and vomiting. The patient was suffering from ulcerative pancolitis since the age of 59. The course of the disease was characterized by frequent severe exacerbations and remissions of short duration. All these years, treatment was based on the administration of mesalazine, azathioprine and corticosteroids. Azathioprine was administered continuously, while the other drugs were administered intermittently for weeks or months each time, the main indication being steroid-dependent disease.

Two months before the appearance of the current symptomatology, she was admitted to our department for severe exacerbation of the underlying UC. She was treated with an intensive intravenous regimen consisting of prednisolone 50mg per day, parenteral administration of fluids and electrolytes and nil by mouth. Colonoscopy performed at that time revealed the presence of severe inflammation of the entire large bowel, while histology of the colonic specimens confirmed the presence of severe inflammation with almost completely ulcerated mucosa. Immunostaining for the presence of cytomegalovirus was negative. The clinical response to treatment was favorable and the patient was discharged with gradually reduced doses of steroids, while continuing treatment with azathioprine.

While the patient was on the aforementioned treatment at home, she suddenly developed high fever, mental confusion and vomiting. Physical examination revealed the presence of nuchal rigidity. The abdomen was slightly tender with normal bowel sounds. Blood pressure was 165/90mmHg, pulse rate 103/min and body temperature 39°C. Brain CT revealed the presence of multiple small infarctions and signs of increased intracranial pressure. With the suspicion of central nervous system infection a lumbar puncture was performed. A slightly cloudy CSF was obtained with a white blood cell count of 220/cc<sup>3</sup>. The CSF glucose level was decreased at 1.6 mmol/L (normal range 2.8- 4.4 mmol/L) and total protein concentration was increased at 1.60 g/L (normal range 0.15- 0.45 g/L). Treatment with ceftriaxone 2g IV three times per day, Zovimax 750mg IV three times a day and Dalacin 600mg IV three times a day was initiated while special cultures from blood and spinal fluid were taken. Arterial blood gases revealed pH 7.40, pCO<sub>2</sub> 33.1, pO<sub>2</sub> 64, and HCO<sub>3</sub> 21.1. The hematocrit was 32.2%, haemoglobin 10.9g/dl, WBC 13,100/mm<sup>3</sup>, platelets 147,000/mm<sup>3</sup>, and ESR 27mm/1<sup>st</sup>h. Serum CRP was 90 mg/l. PCR for mycobacterium tuberculosis and chest x-ray were negative. Because the clinical picture was dominated by the presence of mental confusion, IV administration of Decadron aiming to reduce the cerebral edema was administered. However, despite the administration of antibiotics the patient continued to have high fever and mental confusion. Because the clinical situation was not improved, a second spinal puncture was performed three days later. The white blood cell count was 520x10<sup>6</sup>/L with 78% being neutrophils (normal range 0-5x10<sup>6</sup>/L) and 22% lymphocytes. The CSF glucose level was decreased at 1.5 mmol/L, the total protein concentration was increased at 1.70 g/L and the LDH was 247 U/L. CSF culture identified the presence of *Listeria Monocytogenes*. Based on the results of CSF culture, antibiotic treatment was modified. Ampicilline 3g four times a day

and gentamycin 80mg three times a day were administered intravenously.

During the following days both the level of communication and the general situation of the patient were gradually improved. Corticosteroids were gradually discontinued. A second cerebral computed tomography was unremarkable except of the presence of small infarctions. Blood and urine cultures were negative. The total duration of treatment with ampicilline was 20 days. The patient underwent frequent measurements of the serum levels of gentamycin. Renal function was also under close surveillance. She was finally discharged in good condition.

Few weeks later the underlying large bowel disease recurred possibly due to suspension of administration of steroids. The clinical picture was compatible with severe exacerbation of UC with bloody diarrhea, fever, and fatigue but without any clinical sign of central nervous system involvement. On physical examination the consequences of the long-term administration of corticosteroids (moon face, skin telangiectasias) were obvious. The only available therapeutic strategy we had was to re-administer corticosteroids bearing in mind the recent history of meningitis. Fortunately the patient responded well and she was prepared for elective colectomy. After 4 weeks she underwent a successful ileoanal pouch anastomosis. One year after operation the patient is in a good clinical condition experiencing only 4 to 6 bowel movements per day.

## DISCUSSION

The development of *Listeria* meningitis in patients with UC treated with immunosuppressives and corticosteroids is a rare event if we take into account both the number of patients with UC universally treated with immunosuppressives and corticosteroids and the small number of the relevant descriptions in the international literature. To the best of our knowledge, very few cases with *Listeria* meningitis in patients with UC have been described.<sup>2</sup> By contrast many cases of *Listeria* meningitis in patients receiving biologic agents have been described in the last six years<sup>6</sup> indicating either that the risk of this complication in CD is greater compared to UC or (more importantly) that administration of infliximab predisposes to the development of this complication to a greater extent compared to other immunosuppressive drugs.

Although CNS infection by *Listeria* has many presentations such as encephalitis, brainstem involvement and intracranial abscess, the predominant one in more than 50% of patients, in various series seems to be meningitis.<sup>3,4</sup>

The source and route of infection are not well known and population-based data on the rate of *Listeria* infection is quite few. It has been described that healthy faecal excretors of *Listeria* range from a minimum of 1-62% of office workers to 77% in laboratory workers.<sup>7</sup> It is not clear whether infection in our patient originated from ingestion of contaminated food or from chronic faecal carriage. Therefore, it seems reasonable to suggest that patients with UC on immunosuppressives may avoid consumption of foods such as soft cheeses and unpasteurized dairy products and they must always reheat processed meats until steaming. However, haematogenous spread is thought to be a possible mechanism if the central nervous system is infected.

There are little data on the incidence rate of *Listeriosis* in UC patients. In the case series with *Listeriosis* reported by Samra et al eighteen patients presented of which nine had meningitis and one of them was suffering from UC. In this particular series of patients the infection seemed to be exclusively opportunistic.<sup>2</sup>

The CSF findings in *Listeria* meningitis are reported as variable, a preponderance of polymorphonuclear leucocytes being found in more than 70% of cases. The protein level usually is moderately elevated, while the level of glucose is reduced, although this is not the case in patients suffering from diabetes mellitus. In our patient the findings from CSF were typical of meningitis. However, in a series of patients with *Listeria* meningitis, the cells in the CSF were predominantly lymphocytes in five and polymorphs in four out of nine patients suggesting that lymphocytosis in the CSF, does not exclude bacterial meningitis.<sup>2</sup> The presenting symptoms and physical signs are the same as for any other bacterial meningitis. Concerning the rate of positive CSF cultures among nine patients with meningitis, CSF became positive in five, and negative in four patients.<sup>2</sup> Only 30% of patients had their CSF stained positive for *Listeria* and usually the diagnosis was confirmed only after *Listeria* had been isolated in CSF or blood cultures.<sup>8</sup>

The coexistence of *Listeria* infection and UC exacerbation seems to be incidental. However, *Listeria* infection was confirmed in the resected colon of a patient with fulminant UC using polymerase chain reaction and subsequent southern blot analysis and immunohistochemistry.<sup>9</sup> The authors suggested that *Listeria* infection possibly contributed to the appearance of the serious clinical complication in this particular patient. Furthermore, although *Listeria* DNA was previously detected in the intestine of patients with IBD,<sup>5</sup> in a relevant study similar rate of *Listeria* DNA in endoscopic biopsies of IBD patients and non-IBD controls was found, suggesting that infection by

*Listeria* is not directly involved in the pathogenesis of either UC or Crohn's disease.<sup>10</sup>

During recent years an increasing number of *Listeria* meningitis in patients with CD under treatment with infliximab has been described. It is well known that TNF- $\alpha$  plays an important role in host defence against *Listeria*.<sup>11</sup> This conception is supported by experimental data showing that TNF- $\alpha$  deficient mice are highly susceptible to *Listeria* infection. Infliximab binds and clears soluble TNF- $\alpha$  as well as cell-bound TNF- $\alpha$  on macrophages and T cells, neutralizing its proinflammatory effects and thus reducing the ability of defence against various microorganisms.<sup>12</sup>

It is well established that treatment with corticosteroids and azathioprine may significantly increase the risk of infection.<sup>13</sup> The combination of azathioprine and corticosteroids for a long period of time in our patient probably contributed significantly to the appearance of *Listeria* meningitis.

Patients with *Listeria* infection are usually treated with intravenous ampicillin and gentamicin, for a total period of about three weeks. It is important for the patient's outcome that the addition of gentamicin has a true synergistic effect. Other experts support the use of intravenous penicillin for 2 weeks in immunocompetent patients and 6 weeks for immunocompromised patients. An alternative treatment for patients who cannot tolerate penicillin is sulfamethoxazole combined with trimethoprim. The role of corticosteroids as an adjuvant therapy for meningitis caused by *Listeria* is not known. Finally, it is worth mentioning that *Listeria* utilizes iron as a virulent factor. It is therefore recommended that iron supplementation must be postponed for the whole duration of *Listeria* infection.

It is of interest that although *Listeria* is usually susceptible *in vitro* to many antibiotics the clinical outcome is rather poor. This is partially true because this microorganism is refractory to the bactericidal mechanisms of antibiotics and because few antibiotics reach the cytosol, where *Listeria* is located.<sup>14</sup> Conventional antimicrobial therapy with antibiotics is not satisfactory, particularly if the patients are treated with immunosuppressives. It has been estimated that about 30% of patients with *Listeriosis* die in spite of a rational choice of antibiotics.<sup>15</sup> Fortunately, the majority of patients with *Listeria* meningitis have an uneventful recovery, as in our patient.

**In conclusion,** clinicians should be aware of the possibility of meningitis due to *Listeria Monocytogenes* in patients with UC on immunosuppressives and corticosteroids. They should also consider aggressive investigation and empirical antibiotic treatment in patients with new-onset central nervous system symptoms.

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