

CASE REPORT

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Listeria monocytogenes septicemia and meningitis induced from immunosuppressant treatments in a patient with neuromyelitis optica spectrum disorder: A case report

Ying Hu, Ling Wei, Xingui Chen, Yubao Jiang, Chengjuan Xie, Kai Wang

ABSTRACT

Introduction: The aim of this study is to report a fatal case of *Listeria monocytogenes* septicemia and meningitis complicating azathioprine and glucocorticosteroid treatments during an acute flare of neuromyelitis optica spectrum disorder (NMOSD).

Case Report: A Chinese woman who was diagnosed with NMOSD had been on oral prednisolone and azathioprine for about three years. After her fourth relapse, she was treated with high-dose glucocorticosteroids again, and she soon developed an impaired consciousness, headache, and neck stiffness. Her blood culture was positive for *L. monocytogenes*, and a head computed tomography showed severe hydrocephalus. Although shunt surgery was performed and antibiotics were used, the patient continued to decline and eventually died.

Conclusion: We reported the first Asian case of azathioprine-associated *L. monocytogenes* septicemia in a patient with NMOSD. Physicians should be aware of this serious and potentially lethal side effect when adding

multiple immunosuppressants to the regimen of a patient who is already immunocompromised.

Keywords: Azathioprine, *Listeria monocytogenes*, Meningitis, Neuromyelitis optica

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INTRODUCTION

Listeria monocytogenes (*L. monocytogenes*) is an uncommon pathogen that is a source of sepsis and meningitis in immunocompromised individuals such as neonates, pregnant women, elderly, and patients using of immunosuppressive therapies [1]. The detection and diagnosis of *L. monocytogenes* infection are made by its identification in the blood or cerebrospinal fluid. It is recognized worldwide as an important foodborne pathogen due to its associated high morbidity, hospitalization, and mortality [2].

Neuromyelitis optica spectrum disorders (NMOSDs) are characterized by chronic autoimmune disorders that are associated with central nervous system inflammation and demyelination [3]. Immunosuppressive therapies have been used to treat NMOSDs for years based on the hypothesis that the disease pathogenesis involves a specific antibody binding to astrocytic aquaporin-4 (AQP4) [4]. Based on this hypothesis, azathioprine is

one of the most commonly used immunosuppressive agents used to prevent future exacerbations in patients with NMOSDs. However, azathioprine is also associated with an increased risk of inducing opportunistic infections. Here, we report a case of an NMOSD patient receiving immunosuppressive therapy who developed septicemia and meningitis caused by an infection of *L. monocytogenes*.

CASE REPORT

A 56-year-old Chinese female first developed NMOSD symptoms in 2013, during which she developed paresis in her legs. Magnetic resonance imaging (MRI) and serum autoantibody NMO-IgG studies were supportive of an NMOSD diagnosis that met the Wingerchuk diagnostic criteria [3]. In the subsequent two years, the patient developed at least two relapses with transverse myelitis and she developed incontinence. During each relapse, she was treated with high-dose corticosteroids. Therefore, oral prednisolone (10 mg daily) and azathioprine (100 mg daily) were added to her treatment regimen in 2015. These medications were well tolerated, and she remained clinically stable for nearly four years. However, she experienced a relapse of bladder dysfunction and weakness in her legs at a month after the discontinuation of prednisolone. Assuming a fourth demyelinating event, the patient was referred to our neurological department in 2019.

At the time of admission, blood chemistry showed no signs of systemic infection. The cranial MRI was unremarkable (Figure 1). Her cerebrospinal fluid (CSF) showed a normal leukocyte count and normal protein levels. A spinal MRI revealed an atrophy of the total spine and a transverse myelitis with a T2-hyperintense lesion at T5-8. In this context, intravenous therapy with 500 mg of methylprednisolone was initiated and continued over five days, with concurrent oral azathioprine (150 mg daily) being prescribed. Seven days later, she became sick with diarrhea with 3–4 episodes per day, and a fever of up to 39.6°C. The patient mentioned that she had eaten a watermelon stored in the refrigerator one day before. Urgent laboratory tests showed a white blood cell count of 11.9×10^9 cells/L with 93.3% neutrophils, a C-reactive protein (CRP) level of 130.98 mg/L, and a stool test showed that white blood cells were +++. Based on these characteristic results from here blood and stool samples, sepsis or intestinal infection was suspected, and an empirical antibiotic treatment with cefoxitin was initiated. On the 10th day, a Gram-positive rod bacterium was detected from her blood cultures, after which her antibiotics were adjusted to meropenem.

On the 13th day, when the Gram-positive rod bacterium was identified as *L. monocytogenes*, the patient's temperature was 38.0°C and she showed signs of meningitis. She became confused, her speech was limited to single words only, and she was unable to obey

commands. Her Glasgow Coma Scale score was 7/15. An urgently computed tomography (CT) of the head revealed acute hydrocephalus (Figure 2). Consequently, she was immediately transferred to the intensive care unit and was intubated. A lumbar puncture was performed, which revealed a CSF pressure of 300 mmH₂O. Her CSF was turbid, and the analysis revealed a pleocytosis of 1313×10^6 leukocytes/L (predominantly neutrophils), and a high protein level of 4.1 g/L. The lymphocyte subset analysis revealed that the CD3, CD4, and CD8 T-lymphocyte counts were below the lowest standards. Thereafter, the patient was diagnosed with sepsis and meningitis based on these clinical and laboratory findings. The patient was immediately treated with vancomycin, meropenem, and voriconazole. However, rapid deterioration supervened over hours, and the patient's pupils became fixed and asymmetric. Shunt surgery was performed for her hydrocephalus, and external ventricular drains were placed for CSF drainage in the double lateral ventricle. The serial CSF samples collected demonstrated persistent pleocytosis and infection. The patient remained generally unwell, and a subsequent CT scan revealed diffuse brain edema, ventriculitis, and an obstructed ventricular system (Figure 3). She succumbed to infection and multiple organ failure several days later.

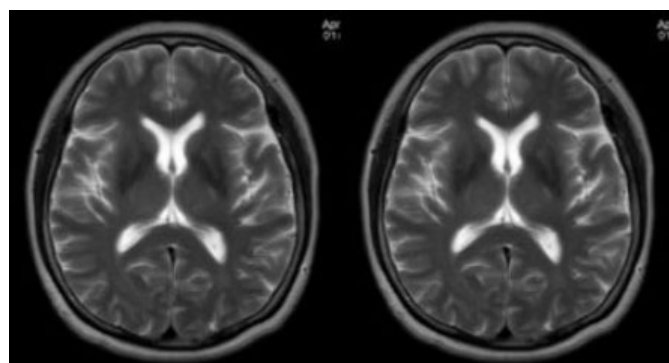


Figure 1: Brain MRI at one day after presentation of symptoms to the department of neurology. T1- and T2-weighted images showing that the ventricles were normal.

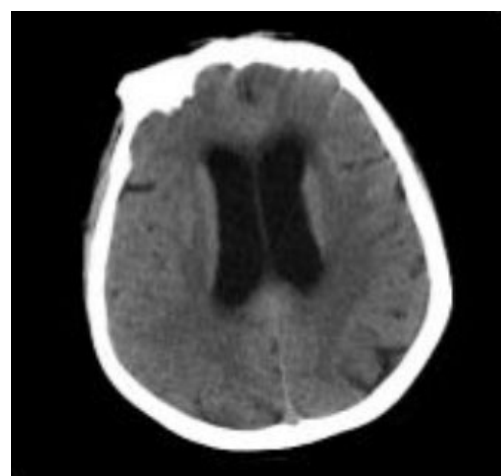


Figure 2: CT brain images on the 13th day after admission showing hydrocephalus of the brain.

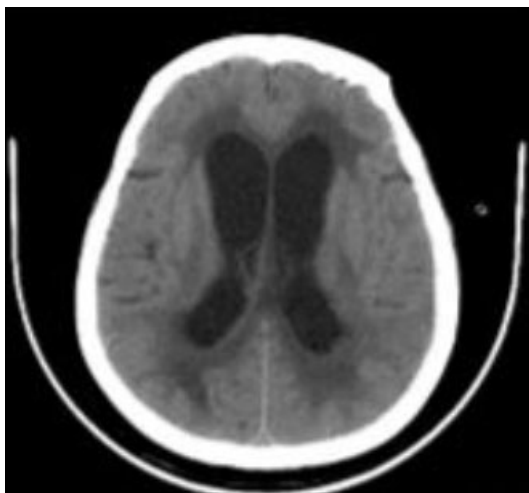


Figure 3: CT brain images before the patient died. Despite adequate placement of an external ventricular drain, there was progressive cerebral edema.

DISCUSSION

Listeria monocytogenes is one of the most severe bacterial foodborne pathogens that infects individuals through ingestion of contaminated food [5]. The resulting sepsis or intrathecal infection carries a high mortality rate among immunosuppressed patients, even following treatment [6]. Low temperatures in refrigerators contribute to the stability of enzymes, which improves the replication of *L. monocytogenes*. The patient in our present case report developed clinical symptoms the day after she had clear exposure to foodstuffs stored in the refrigerator. The ingestion of contaminated food, especially stored at a low temperature, is thought to have been the principal route of *L. monocytogenes* transmission in this patient. Therefore, we recommend that patients undergoing immunosuppressive treatments avoid potentially contaminated food without heating or pasteurization.

Listeria monocytogenes binds primarily to gastrointestinal epithelial cells via the host protein, cadherin [7]. As a result, in our present case report, enteritis was the first symptom of *L. monocytogenes* infection. After invasion into host cells, the bacterium has a propensity to initiate a cell-mediated immune response. Because of the intracellular lifecycle, bacterial clearance is entirely dependent on the secondary activation of cytolytic CD8 T-cells [8]. Therefore, conditions associated with impaired cellular immunity are risk factors for *L. monocytogenes* infection.

An increased risk of opportunistic infections is well documented in association with immunosuppressant treatments—including steroids, azathioprine, and biological therapies—via dampening the body's cellular immune response [9]. In patients with multiple sclerosis treated with alemtuzumab, the risk of listeriosis is in the range of 0.1% [10]. However, analogous reports in

patients with NMOSDs treated with azathioprine are relatively rare. Azathioprine is an antimetabolite that interferes with purine pathways used in DNA synthesis and cellular multiplication, especially in terms of B- and T- lymphocytic proliferation [11]. CD4 and CD8 T cells are essential for intracellularly controlling infections. Therefore, conditions associated with depletion of such cells from the circulation are risk factors for *L. monocytogenes* infection.

In our patient, there was a strong temporal relationship between high-dose corticosteroids combined with azathioprine treatment and the onset of neurologic symptoms, suggesting that corticosteroids also played a decisive role in the development of this opportunistic infection. Corticosteroids can cause immunosuppression in a variety of ways, including inhibition of phagocytosis and intracellular killing of pathogens [12]. Two reports have described the occurrence of *L. monocytogenes* in patients with ulcerative colitis treated with a combination of oral prednisolone and azathioprine [6, 13]. Unlike our patient, in these previous cases, the patients all recovered rapidly and completely upon treatments with antibiotics. This may partly be due to these cases employing lower doses of corticosteroids and azathioprine and therefore including milder side effects. This case report suggests that patients are at a higher risk of *L. monocytogenes* infection if they are taking high-dose corticosteroids or multiple medications to suppress immune responses.

To the best of our knowledge, this is the first case report in which enteritis induced by *L. monocytogenes* worsened in an Asian NMOSD patient who was receiving corticosteroids and azathioprine, which led to septicemia and meningitis.

CONCLUSION

In conclusion, *L. monocytogenes* can exacerbate inflammation in NMOSD, enter the mesenteric lymph nodes and then the blood stream, resulting in bacteremia and meningitis in patients with an immunosuppression. Our case report is pointing toward three possible associations with invasive listeria infection: autoimmune disease, treatment with steroids and azathioprine, and finally the insanitary food.

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Author Contributions

Ying Hu – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Ling Wei – Conception of the work, Design of the work, Acquisition of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Xingui Chen – Design of the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Yubao Jiang – Design of the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Chengjuan Xie – Design of the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Kai Wang – Design of the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Guarantor of Submission

The corresponding author is the guarantor of submission.

Source of Support

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Written informed consent was obtained from the patient for publication of this article.

Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.

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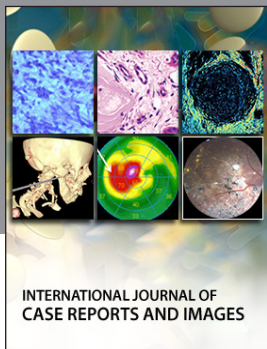
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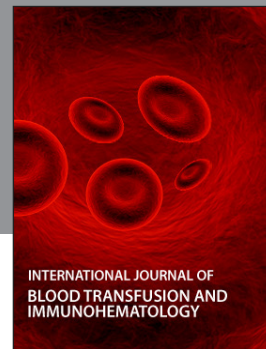
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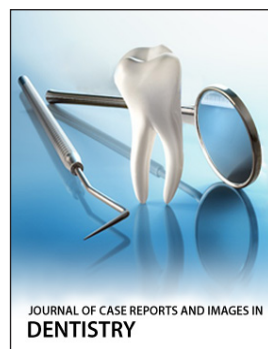
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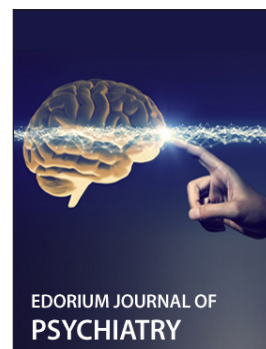
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