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Drastic Therapy for Listerial Brain Abscess Involving Combined Hyperbaric Oxygen Therapy and Antimicrobial Agents

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Background *Listeria monocytogenes* (*L. monocytogenes*) is a rare causative pathogen of brain abscess that is often found in immunocompromised patients. Although patients with supratentorial listerial abscesses showed a longer survival with surgical drainage, the standard therapy for patients with subtentorial lesions has not been established.

Case Report We report herein a patient with supra- and subtentorial brain abscesses caused by *L. monocytogenes* infection. These abscesses did not respond to antibiotics, and his symptoms gradually worsened. Drainage was not indicated for subtentorial lesions, and the patient was additionally treated with hyperbaric oxygen therapy, which dramatically reduced the volume of abscesses and improved the symptoms.

Conclusions This is the first report of drastic therapy for a patient with listerial brain abscesses involving combined antibiotics and hyperbaric oxygen therapy. The findings suggest that hyperbaric oxygen therapy is a good option for treating patients with deep-seated listerial abscesses and for who surgical drainage is not indicated. **J Clin Neurol 2014;10(4):358-362**

Key Words brain abscess, *Listeria monocytogenes*, subtentorial lesions, surgical drainage, hyperbaric oxygen therapy, antimicrobial agents.

Introduction

Listeria monocytogenes (*L. monocytogenes*) is a facultative anaerobic, Gram-positive bacillus that is commonly isolated from the soil, vegetables, and wild or domestic animals. *L. monocytogenes* has a special tropism for the central nervous system (CNS). Meningoencephalitis is the most common CNS manifestation of listerial infection, whereas brain abscess is rare, representing 1–10% of all CNS listerioses.¹ Listerial brain abscess is often found in immunocompromised patients with an underlying illness or who are undergoing immunosuppressive therapy.

Listerial brain abscess has a high mortality and requires extensive treatment with antibiotics, drainage if necessary, and a reduction in immunosuppressives. It can be supra- and subtentorial; while a review of patients with supratentorial listerial abscesses revealed that the survival rate was higher among those provided with surgical drainage,² the standard therapy for patients with subtentorial lesions has not yet been established. We report herein a patient with supra- and subtentorial brain abscesses due to *L. monocytogenes* infection who was treated with combined antibiotics and hyperbaric oxygen (HBO) therapy instead of surgical drainage.

Case Report

A 68-year-old male noticed headaches on July 8, 2012, and then right hemiparesis on July 19 of the same year. The primary care physician diagnosed stroke, and he was admitted to

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hospital. He had no medical history of head trauma, sinusitis, or diabetes, but he drank 1,800 mL of a distilled spirit (equivalent to 330 g of ethanol) with blue cheese every day, and had alcoholic liver cirrhosis (Child-Pugh grade B). He was febrile (39.0°C) and had become progressively paralyzed on the right side of his body. Brain magnetic resonance imaging (MRI) disclosed several ring-enhancing lesions in the brainstem and cerebral hemispheres. A cerebrospinal fluid (CSF) examination revealed pleocytosis, and a blood examination revealed an increased titer of *Aspergillus* antigen without inflammatory reaction; the (1→3)- β -D-glucan test was negative.

Bacterial cultures taken from two independent vessels grew *L. monocytogenes*, which led to a diagnosis of multiple brain abscesses due to *L. monocytogenes* infection. He was treated with ampicillin (ABPC; 2 g every 4 h i.v.) and voriconazole (200 mg/day), but he developed consciousness disturbance and complete right-sided hemiparesis. Follow-up brain MRI disclosed extended lesions, and the patient was transferred to our hospital. Upon admission he had a body temperature of 36.9°C, and a physical examination revealed neither superficial lymphadenopathy nor hepatosplenomegaly. A neurologic examination revealed that he was in a comatose state (score on the Japan Coma Scale of 30–200). Right blepharoptosis and anisocoria (3.0 mm on the right and 4.0 mm on the left) was

observed. The left light reflex was attenuated, while that on the right was preserved. His oculoccephalic reflex was positive. The right hemiparesis was severe but without muscular waste and fasciculation. The tendon reflexes were exaggerated in the right upper and lower limbs, but without pathologic reflexes. Neither neck stiffness nor Kernig's sign was detected. Laboratory data revealed no inflammatory reaction such as leukocytosis or elevation of C-reactive protein, but pleocytosis was evident in the CSF: 101 cells/mm³ (96.6% mononuclear and 3.4% polymorphonuclear cells); protein, 201 mg/dL; and glucose, 58 mg/dL (plasma glucose, 78 mg/dL). No pathogenic bacteria grew in bacterial cultures of the CSF, blood, urine, and a nasopharyngeal swab.

Brain MRI disclosed several ring-enhancing lesions on the left cerebral hemisphere and brainstem (Fig. 1A and B). High-intensity signals were present inside the mass lesions in diffusion-weighted imaging (Fig. 1C). Susceptibility-weighted imaging disclosed a dual rim sign, defined as two concentric rims at the lesion margins, with the outer rim being hypointense and the inner rim hyperintense relative to the cavity contents (Fig. 1D). MR spectroscopy revealed no elevation of choline in the lesions. Positron-emission tomography (PET) demonstrated no uptake of 2-[fluorine-18]-fluoro-2-deoxy-D-glucose, suggesting the absence of malignancy.

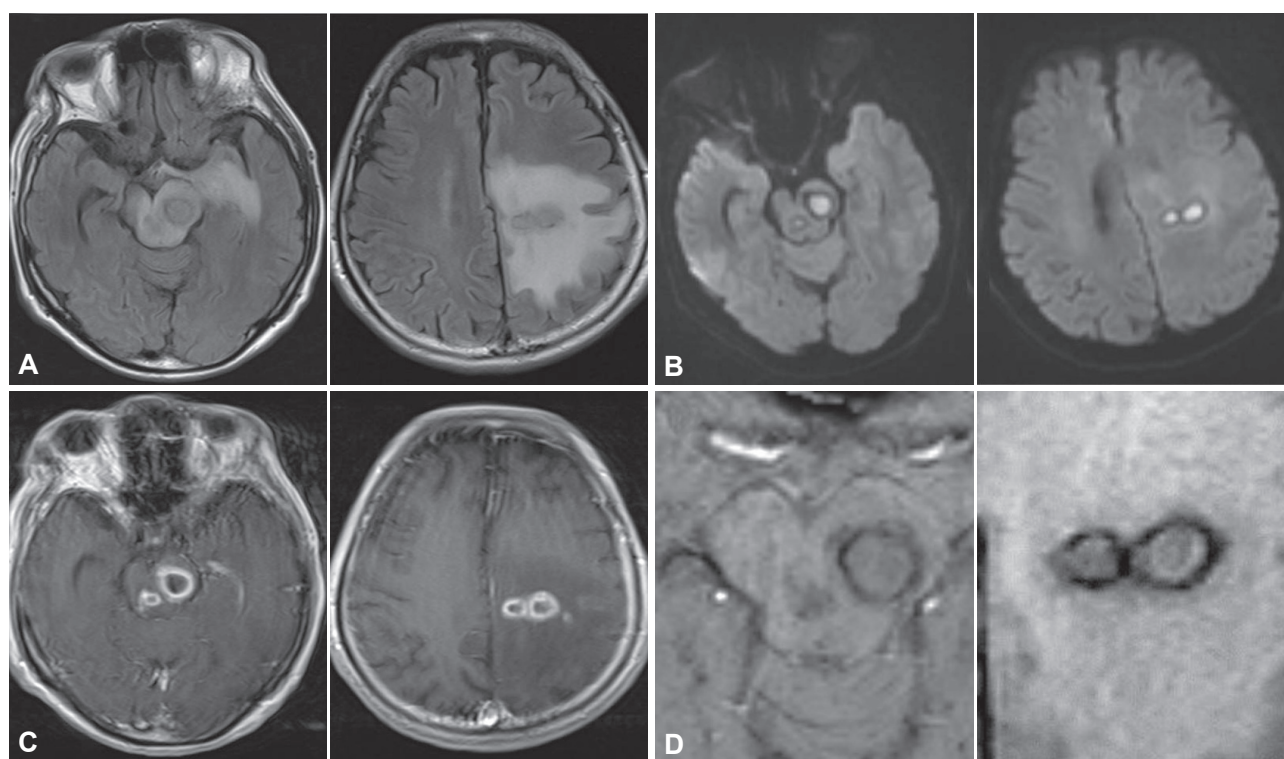


Fig. 1. Brain magnetic resonance imaging on admission. A: Fluid-attenuated inversion-recovery images disclosed iso- to hypointensity lesions in the midbrain and left cerebral hemisphere with surrounding edema. B: T1-weighted images with gadolinium enhancement showed ring enhancement in these lesions. C: High-intensity signals were present inside in the lesions in diffusion-weighted imaging. D: Susceptibility-weighted imaging revealed a dual rim sign: defined as two concentric rims at the lesion margins, with the outer rim being hypointense and the inner rim hyperintense relative to the cavity contents.

Treatment with ABPC (2 g every 4 h i.v.) and voriconazole (100 mg every 12 h i.v.) was continued. Diagnostic and therapeutic drainage for brainstem lesions is not favored at our neurosurgical department, and so the patient instead underwent HBO therapy (100% O₂ at 196.1 kPa abs at 1 h/day, for 25 days) from August 17. After the treatment, his consciousness status and pleocytosis gradually improved. The anisocoria had resolved by August 20, and voluntary movements of the right upper and lower limbs were possible by September 5 (Fig. 2). Since the lesions were dramatically ameliorated on follow-up MRI, we terminated the voriconazole and ABPC therapy on October 3 and 10, respectively. The patient was transferred to another hospital for rehabilitation on October 17.

Discussion

We have reported herein a patient with supra- and subtentorial brain abscesses caused by *L. monocytogenes* infection who was treated concurrently with antibiotics and HBO therapy, resulting in reduction of the volume of the abscesses and improvement of clinical symptoms. The diagnosis of multiple brain abscesses due to *L. monocytogenes* infection was reached for the following reasons:

- 1) The patient presented a remittent fever with at a maximum temperature of 39°C.
- 2) Brain MRI at admission disclosed ring-enhancing lesions in the supra- and subtentorial regions, and SWI revealed a homogeneous dual rim sign, suggesting the presence of brain abscess.³
- 3) *L. monocytogenes*, which tends to form abscesses in the brainstem region, grew in blood bacterial cultures performed at first admission.

4) PET revealed no malignancy in the lesions.

While the blood examination disclosed an increased titer of *Aspergillus* antigen, the spread of *Aspergillus* species in the CNS generally takes place via the sinuses and is observed primarily in the frontal and temporal lobes.⁴ Furthermore, the negative (1→3)-β-D-glucan test suggested that the brain abscesses in this patient were not related to *Aspergillus* infection, which is usually associated with a high frequency of positivity for this test.

Listeria enters the human host via the intestines after the ingestion of contaminated food, and spreads to distant tissues via the lymph and blood, using mononuclear phagocytes to disseminate throughout the host from its sites of entry.^{5,6} *L. monocytogenes* is found most frequently in soft cheeses such as blue cheese and infection is usually found in immunocompromised patients such as pregnant women, infants, and babies. However, this patient consumed large amounts of both blue cheese and alcohol, and we therefore believe that he developed listerial brain abscesses. Listerial brain abscess has a high mortality rate, estimated to be approximately 40%.⁷ Of note, CSF cultures tested positive in 25% of cases, while blood cultures are usually only positive on repeated cultures.⁸ Abscesses in deep locations such as the thalamus, pons, and medulla oblongata are considered pathognomonic for listerial brain abscess because *L. monocytogenes* spreads via the blood circulation rather than by direct invasion.²

The clinical practice guidelines of the Infectious Diseases Society of America recommend the use of ABPC plus gentamicin as a first-line treatment for *L. monocytogenes* infection.⁹ This recommendation was based on the synergistic increase in the bactericidal activity observed *in vitro* with a combination of ABPC and gentamicin.¹⁰ In contrast, a recent study revealed

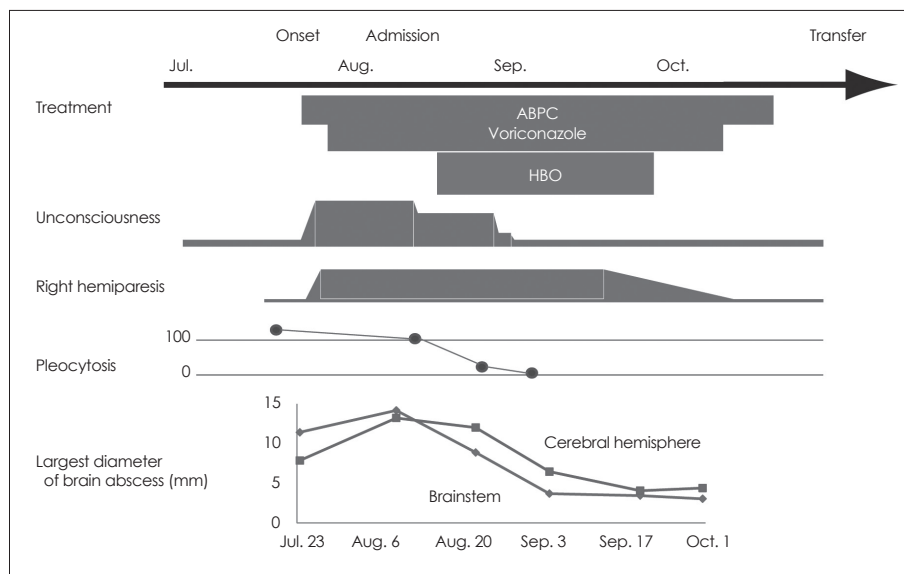


Fig. 2. Clinical course of the patient. Hyperbaric oxygen therapy (HBO; 100% O₂ at 196.1 kPa abs at 1 h/day for 25 days) was performed between August 17 and September 20. After the treatment, the patient's consciousness status, right hemiparesis, and pleocytosis gradually improved. The diameter of the brain abscesses was dramatically reduced. ABPC: ampicillin.

that the use of combination therapy increased not only the associated renal toxicity but also the mortality in listeriosis.¹¹ No randomized clinical trial has compared amoxicillin or ABPC alone versus amoxicillin or ABPC plus gentamicin in cases with listerial brain abscess; we therefore did not choose these combination therapies.

While a review of patients with supratentorial listerial abscesses revealed that the survival rate was higher among patients provided with surgical drainage,⁸ the standard therapy for patients with subtentorial lesions has not yet been established. There are a few case reports of successful stereotactic biopsy and drainage in patients with listerial brainstem abscess, resulting in a reduction in the lesion size, identification of the pathogen, and survival.¹² As mentioned above, listerial brain abscesses are typically infections of deeper brain structures such as the thalamus, pons, and medulla, where other bacteria rarely cause abscesses.⁸ It is therefore mandatory to establish a standard therapy for listerial brainstem abscess that does not involve surgical drainage.

The treatment of intracranial abscesses with HBO was first introduced in the 1980s.^{13,14} There are several possible mechanisms by which HBO therapy could have ameliorated the brain abscesses in the present case. First, the production of reactive oxygen species by HBO may have activated the neutrophils and damaged any aerobic and facultative anaerobic bacteria, such as *L. monocytogenes*. Second, HBO therapy may have increased the cerebral arterial oxygen pressure, reduced the intracranial pressure by inducing the contraction of blood

vessels, and thus protected the patient against secondary brain injury. Finally, although *L. monocytogenes* is a facultative anaerobic bacterium, which is thought to be natively resistant to HBO,¹⁵ we assume that concurrent therapy with HBO and antimicrobial agents was responsible for the good prognosis in the present case.

There are some factors that need to be considered when applying HBO therapy to patients with brain abscess. First, patients are required to maintain a resting position during the treatment. Second, unconscious patients tend to suffer from middle ear barotraumas due to the pressure inside the middle ear not being equalized with the external pressure.¹⁶ We resolved this problem by applying tympanostomy with sedation before the treatment.

A summary of cases of patients with listerial abscesses who were treated by medication alone and their clinical outcomes are described in Table 1. Three of the five patients died, while the other two survived without sequelae (in addition to the present case), who were treated with concurrent therapy with HBO and antimicrobial agents. Lampl et al.¹³ postulated that HBO should be considered with the following patient criteria: multiple brain abscesses, abscess in a deep or dominant location, early-stage abscess without a need for surgical intervention, poor patient condition, and anaerobic or miscellaneous findings from abscess material.

This is the first report of drastic therapy for a patient with listerial brain abscesses who was treated with combined antibiotic and HBO therapy. The findings suggest that HBO thera-

Table 1. Review of case reports of treatments without surgical drainage in the literature

| Age/gender | Underlying diseases | Immuno-suppressant | Antibiotics | Hyperbaric oxygen therapy | Outcome | References |
|------------|--|-----------------------|--|---------------------------|----------------------------|----------------------------------|
| 71/M | Diabetes mellitus, rheumatic heart disease, endocarditis | None | ABPC for 7 days, GM for 8 days | No | Death | Eckburg et al. ⁸ 2001 |
| 58/F | Immunoblastic lymphadenopathy | Steroid, chemotherapy | ABPC for 8 weeks | No | Recovered without sequelae | Maewawa et al. ⁷ 2002 |
| 47/M | Acquired immunodeficiency syndrome, multiple hepatic abscess | Steroid | ABPC, GM, VCM | No | Death | Cone et al. ¹⁷ 2003 |
| 56/F | Autoimmune hepatitis, primary biliary cirrhosis | Steroid, azathioprine | ABPC for 6 weeks, GM for 14 days | No | Recovered without sequela | Cone et al. ¹⁷ 2003 |
| 70/M | Alcohol abuse | Steroid | ABPC, GM, VCM | No | Death | Cone et al. ¹⁷ 2003 |
| 68/M | Alcohol abuse, liver cirrhosis | None | ABPC for 11 weeks, voriconazole for 10 weeks | Yes | Recovered without sequelae | Present case |

ABPC: ampicillin, GM: gentamicin, VCM: vancomycin.

py is a good option for patients with deep-seated listerial abscesses who are not indicated for surgical drainage.

Conflicts of Interest

The authors have no financial conflicts of interest.

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