

Listeria monocytogenes Meningoencephalitis Mimicking Stroke in a Patient with Chronic Lymphocytic Leukemia

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Received: May 4, 2013 / Published online: July 2, 2013

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ABSTRACT

Introduction: *Listeria monocytogenes* is an important opportunistic pathogen affecting patients with immunosuppression and shows a high tropism for the central nervous system.

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The clinical manifestations of central nervous system listerial infections are variable and represent a diagnostic challenge.

Case Report: The authors report the case of a 59-year-old woman who was admitted for confusion, agitation, and right-lower extremity weakness. The patient was treated for 3 months with fludarabine and 2 months with corticosteroids for chronic lymphocytic leukemia and hemolytic anemia, respectively. At the time of admission, the neurological examination revealed grade 4 right-lower extremity weakness with reflex asymmetry and right-sided Babinski sign; no signs of meningeal irritation were detectable. Physical examination was notable for grade 1 obesity and subfebrility. The cerebral computed tomography scan demonstrated a hypodense lesion in the left frontal lobe. Cerebral magnetic resonance imaging revealed a hyperintense lesion in the left frontal lobe with extension toward the basal ganglia (T2 and Fluid-Attenuated Inversion Recovery [FLAIR] sequences), and small nodular enhancing lesions after gadolinium infusion in the affected territory. Blood analyses revealed pancytopenia and elevated liver enzymes. During the second day after



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admission, the patient developed fever and neurological examination revealed signs of meningeal irritation. The cerebrospinal fluid (CSF) analyses revealed: red blood cells 24 cells/mm³; white blood cells 829 cells/mm³ (76% lymphocytes, 22% neutrophils, 2% monocytes); protein level 111.2 mg/dL; glucose level 10.2 mg/dL. Empiric anti-infection treatment was started with intravenous ceftriaxone, ciprofloxacin, aciclovir, and fluconazole. Both blood cultures and CSF cultures were positive for *L. monocytogenes*. The antimicrobial regimen was changed to ampicillin. The clinical and imaging outcome was excellent.

Conclusion: The supratentorial focal lesions secondary to *Listeria meningoenzephalitis* are rare. The cases with focal neurological signs without fever at onset can resemble stroke.

Keywords: Chronic lymphocytic leukemia; Cerebrospinal fluid; *Listeria monocytogenes*; Meningoenzephalitis; Neurology; Stroke

INTRODUCTION

Listeria monocytogenes is a foodborne pathogen affecting mostly newborns, pregnant women, and non-pregnant adults with either primary or secondary immunosuppression conditions, especially cellular immunity disturbances. *Listeria monocytogenes* shows a high tropism for the central nervous system (CNS). The most frequent neurological manifestation is meningitis. Meningoenzephalitis and enzephalitis (cerebritis), which can progress to brain abscess and rhombencephalitis (brainstem enzephalitis), are less common [1–3].

Chronic lymphocytic leukemia (CLL) is the most common leukemia that occurs in adulthood and frequently is accompanied by a

multitude of immune abnormalities. Defects in both the cell-mediated and humoral-mediated immunity are responsible for the disease specific complications of CLL, including the infectious complications [4–6]. Beside the disease-related immune abnormalities, further immunosuppression related to therapy with cytotoxic drugs, steroids, and monoclonal antibodies predisposes patients with CLL to infections [7].

Cases with focal neurological signs without fever and meningeal signs at onset represent a diagnostic challenge. The authors present a case of *L. monocytogenes* meningoenzephalitis mimicking anterior cerebral artery territory stroke. The diagnosis was based on cerebrospinal fluid (CSF) analysis, positive CSF and blood culture, and cerebral imaging findings.

CASE REPORT

A 59-year-old hypertensive white female was diagnosed with CLL in 2009. Informed consent was obtained from the patient for being included in the study.

Chemotherapy with fludarabine was initiated 3 months earlier and corticotherapy with methylprednisolone 2 months earlier for hemolytic anemia secondary to fludarabine treatment. The patient presented with a 24 h history of confusion, agitation, and mild right-lower extremity weakness.

Physical examination was notable for grade 1 obesity and subfebrility (99.32 °F; 37.4 °C).

Neurological examination revealed a grade 4 right-lower extremity weakness with reflex asymmetry and right-sided Babinski sign. No signs of meningeal irritation were detectable.

Laboratory findings included: white blood cell (WBC) count of $3.5 \times 10^3/\mu\text{L}$; hemoglobin

7.1 g/dL; hematocrit 21.5%; platelets $109 \times 10^3/\mu\text{L}$; aspartate aminotransferase 59 U/L; alanine transaminase 79 U/L. Serum glucose, urea nitrogen, creatinine, bilirubin, sodium, and potassium were normal.

Cerebral computed tomography (CT) scan revealed a hypodense lesion in the left frontal lobe suggestive of an ischemic stroke (Fig. 1).

During the second day after admission, the patient developed fever (101.12 °F; 38.4 °C) and neurological examination revealed signs of meningeal irritation (positive Kernig's sign).

Cerebral magnetic resonance imaging (MRI) revealed a hyperintense lesion in the left frontal lobe with extension toward the basal ganglia (T2 and Fluid-Attenuated Inversion Recovery [FLAIR] sequences) (Fig. 2), and small nodular

enhancing lesions after gadolinium infusion in the affected territory (Fig. 3).

Lumbar puncture was performed on the second day and the CSF analysis revealed the following abnormalities: red blood cells (RBCs) 24 cells/mm³; WBCs 829 cells/mm³ (76% lymphocytes, 22% neutrophils, 2% monocytes); protein level 111.2 mg/dL; glucose level 10.2 mg/dL (serum glucose 86 mg/dL). CSF and blood samples were sent to laboratory for culture. Empiric anti-infection treatment was started with intravenous (i. v.) ceftriaxone, ciprofloxacin, aciclovir, and fluconazole. The neurological status of the patient was unchanged 2 days after the initiation of anti-infection therapy and the patient presented septic fever. CSF

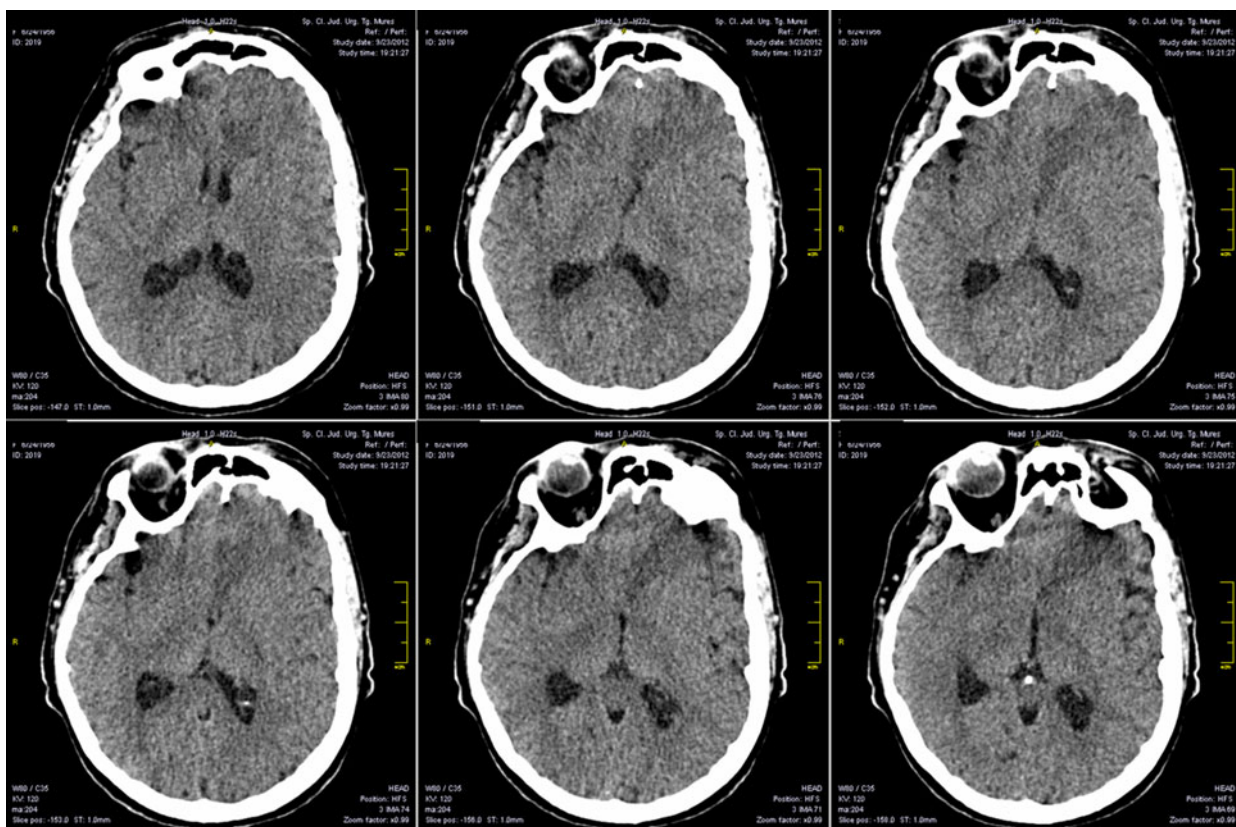


Fig. 1 Cerebral CT scan showing a hypodense lesion in the left frontal lobe. *CT* computed tomography

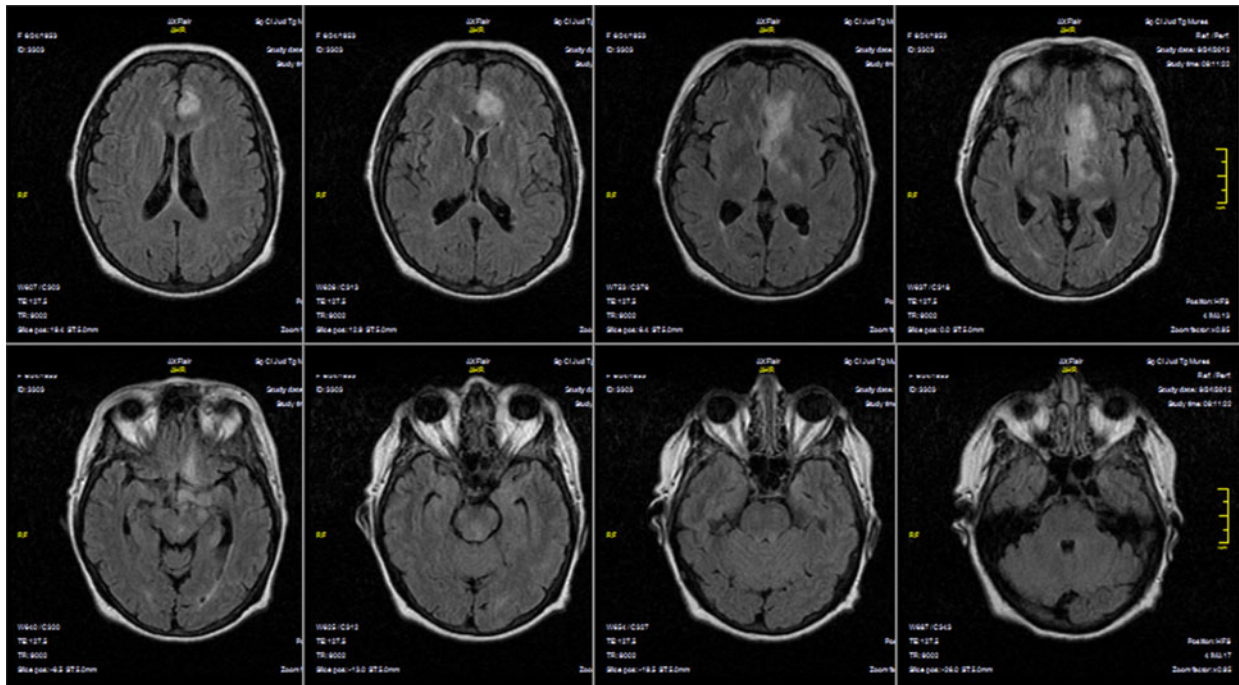


Fig. 2 Cerebral MRI. FLAIR sequences showing a hyperintense lesion in the left frontal lobe with extension toward the basal ganglia. *FLAIR* Fluid-Attenuated Inversion Recovery, *MRI* magnetic resonance imaging

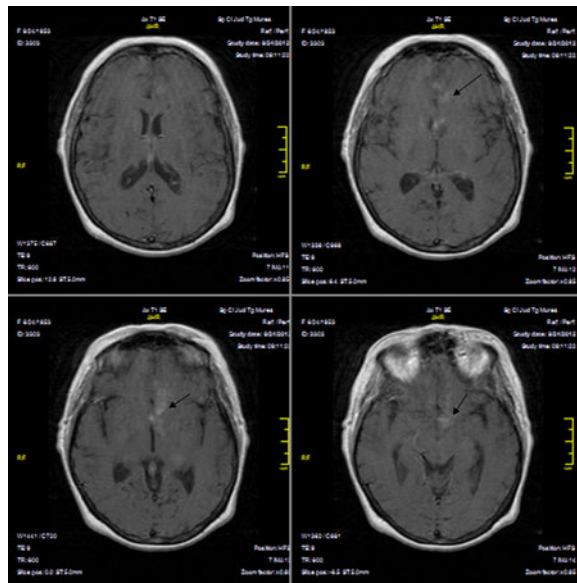


Fig. 3 Cerebral MRI. T1-weighted images after gadolinium administration showing some enhancing nodular lesions parasagittally in the left cerebral hemisphere. *MRI* magnetic resonance imaging

examination was negative for fungal infections, *Mycobacterium tuberculosis*, and JC virus. Both blood cultures and CSF cultures were positive

for *L. monocytogenes*. The microbial identification was performed with Vitek 2 automated analyzer system (bioMérieux, Marcy l'Etoile, France). The culture was not verified by molecular methods. The serotype of *L. monocytogenes* was not determined. There was no history of consumption of high-risk foods for *L. monocytogenes* infection (such as soft-cheeses made with unpasteurized milk, frankfurters, sliced deli meats, etc.) in the past 10–14 days. The infection was not associated with any known food outbreaks.

The diagnosis of *Listeria meningoenzephalitis* was established and antibiotic therapy with ampicillin was started (12 g/day). Forty-eight hours after the initiation of antibiotic treatment with ampicillin, the patient was afebrile with significantly improved neurological status. CSF analysis after 1 week of treatment revealed: RBCs 0 cells/mm³; WBCs 80 cells/mm³; protein level 73 mg/dL; glucose level 49 mg/dL (serum glucose 90 mg/dL). One month

later, the neurological examination of the patient was normal.

DISCUSSION

Listeria monocytogenes is an important bacterial agent which infects patients with immunosuppression. Immunity to this bacterium relies mainly on T-cell lymphokine activation of macrophages. Interleukin-18 plays a role in protection against listeria by enhancing bacterial clearance and by stimulating macrophages to secrete tumor necrosis factor and nitric oxide. Factors that impair macrophage survival and function are associated with high susceptibility to listerial infection [8–11].

In CLL, both the humoral and cellular immunity are affected. There are cellular qualitative and quantitative defects in B-cells, T-cells, NK cells, neutrophils, and the monocyte and/or macrophage lineage that are inherent to the disease process and to its progression. These immunological defects are further complicated by the immunosuppressive properties of the drugs used in the treatment of CLL [4].

It is estimated that up to 80% of the patients with CLL will develop infectious complications during their disease course, and these infections are responsible for up to 60% of deaths [4]. Patients undergoing chemotherapy are not only at risk of acquiring infections but also at risk of reactivation of latent infections. Patients treated with potent drugs, such as purin analogues (e.g., fludarabine) and monoclonal antibodies, are predisposed to infections with opportunistic pathogens, such as *Pneumocystis jirovecii*, *L. monocytogenes*, herpes viruses, JC virus, fungus (*Candida*, *Cryptococcus*, *Aspergillus*), and *Toxoplasma gondii* [4, 12].

Glucocorticoid therapy is an important predisposing factor to listeria infection. In a large case series of CLL patients, listeria infection occurred in seven of 248 patients treated with prednisone and fludarabine, and no listerial infection occurred in 160 patients treated with fludarabine alone or in 387 patients treated with conventional chemotherapy [13].

The most common type of CNS damage in listerial infection is meningitis. In more rare cases the damage can be meningoencephalitis or encephalitis (mainly rhombencephalitis) [14]. The clinical presentation of *Listeria* meningoencephalitis ranges from mild illness with fever and mental state changes to fulminant disease with coma. The meningeal signs are not present in all cases. In a large case series of 820 patients, 42 % presented without signs of meningeal irritation. The presence of focal neurological signs (cranial nerve palsies, ataxia, tremor, hemiparesis) indicates an encephalitic component [15].

Cases without fever at onset and focal neurological signs can resemble stroke. Elzière et al. [16] published a case with left progressive hemiparesis without fever at hospital admission. This patient developed fever only 2 days after hospital admission and represented a diagnostic challenge.

CSF analyses in CNS infections with listeria show pleocytosis. Due to the substantial number of lymphocytes (>25%), and the CSF pattern can suggest tuberculosis meningitis. The CSF protein level is moderately elevated in almost all patients, the CSF glucose level is reduced in 40% of cases [17]. The gram stain has a low sensitivity and may resemble pneumococci or diphtheroids [15]. RBCs can be present in the CSF of patients with listeria CNS infection in the absence of a CNS bleed or traumatic tap. In this case, the differential

diagnosis must include the herpes simplex virus encephalitis and tuberculous meningitis [17].

The positivity of CSF and blood cultures is variable. Negative CSF culture results occur in >11–30% of patients with *L. monocytogenes* meningitis [18]. The blood cultures are positive in approximately 50% of cases with CNS infection. Positive blood cultures rarely occur in the presence of negative CSF cultures [18].

For differential diagnostic reasons, the present case would have benefitted from the analysis of reibergrams or CSF/serum quotient graphs, which are diagrams that analyze in an integrated way both the function of the blood-CSF barrier and intrathecal protein synthesis. The calculation of reibergrams connote the determination of albumin and immunoglobulin (Ig)A, IgM, and IgG in serum and CSF. In addition to the aforementioned Ig calculations, some authors include in the analysis the IgE and IgG subclasses, and C3 and C4 complement fractions in order to reveal immunodeficiencies, autoimmune, and infectious diseases [19–22].

For the detection of the cerebral lesions secondary to listerial infection, MRI is more sensitive than CT. MRI reveals a high signal intensity in T2 and FLAIR sequences, and enhancing lesions in T1-weighted images after administration of gadolinium [16, 23].

In the treatment of listerial CNS infection, ampicillin is the first-line agent. There is an important synergistic effect between aminoglycoside and ampicillin or penicillin. Many clinicians recommend the addition of an aminoglycoside to ampicillin for at least the first week of treatment. Bacteremic patients with normal CSF may be treated for 2 weeks. Patients with brain abscess, encephalitis, or rhombencephalitis should be treated for at least 6 weeks. In cases of penicillin hypersensitivity, trimetoprim-sulfametoxazol is the treatment of

choice. Cephalosporins have limited activity against listeria. Vancomycin, imipenem, and meropenem also have been used successfully to treat cases of listeriosis. Some newer quinolones and linezolid show good in vitro activity [24]. The value of adjunctive corticosteroids in listerial infection is not known [24–27].

The prognosis of listerial infections is highly variable. CNS infection is an important risk factor for morbidity and mortality. Neurological sequelae are common among the survivors of CNS infections [28–30].

CONCLUSION

The supratentorial focal lesions secondary to *Listeria* meningoencephalitis are rare. The cases with focal neurological signs without fever at onset can resemble stroke.

ACKNOWLEDGMENTS

No funding or sponsorship was received for this study or publication of this article. Dr. Bajkó is the guarantor for this article, and takes responsibility for the integrity of the work as a whole.

Conflict of interest. Zoltán Bajkó declares no conflict of interest. Rodica Bălașa declares no conflict of interest. Smaranda Maier declares no conflict of interest. Anca Moțățăianu declares no conflict of interest. Andrada Treabă declares no conflict of interest. Ioan Macarie declares no conflict of interest. Cristina Gârbovan declares no conflict of interest. Carmen Chiriac declares no conflict of interest.

Compliance with Ethics Guidelines. Informed consent was obtained from the patient for being included in the study.

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REFERENCES

- Gellin BG, Broome CV. Listeriosis. *JAMA*. 1989;261:1313–20.
- Aladro Y, Ponce P, Santullano V, Angel-Moreno A, Santana MA. Cerebritis due to *Listeria monocytogenes*: CT and MR findings. *Eur Radiol*. 1996;6:188–91.
- Mailles A, Lecuit M, Goulet V, Leclercq A, Stahl JP. National Study on Listeriosis Encephalitis Steering Committee. *Listeria monocytogenes* encephalitis in France. *Med Mal Infect*. 2011;41:594–601.
- da Lopes Silva R. Spectrum of neurologic complications in chronic lymphocytic leukemia. *Clin Lymphoma Myeloma Leuk*. 2012;12:164–79.
- Hamblin AD, Hamblin TJ. The immunodeficiency of chronic lymphocytic leukaemia. *Br Med Bull*. 2008;87:49–62.
- Dearden C. Disease-specific complications of chronic lymphocytic leukemia. *Hematology Am Soc Hematol Educ Program*. 2008:450–456.
- Nosari A. Infectious complications in chronic lymphocytic leukemia. *Mediterr J Hematol Infect Dis*. 2012;4:e2012070.
- Southwick FS, Purich DL. Intracellular pathogenesis of listeriosis. *N Engl J Med*. 1996;334:770.
- Neighbors M, Xu X, Barrat FJ. A critical role for interleukin 18 in primary and memory effector responses to *Listeria monocytogenes* that extends beyond its effects on Interferon gamma production. *J Exp Med*. 2001;194:343–54.
- Helmy KY, Katschke KJ Jr, Gorgani NN. CR1g: a macrophage complement receptor required for phagocytosis of circulating pathogens. *Cell*. 2006;124:915–27.
- Joseph SB, Bradley MN, Castrillo A. LXR-dependent gene expression is important for macrophage survival and the innate immune response. *Cell*. 2004;119:299–309.
- Morrison VA. Infectious complications of chronic lymphocytic leukaemia: pathogenesis, spectrum of infection, preventive approaches. *Best Pract Res Clin Haematol*. 2010;23:145–53.
- Anaissie E, Kontoyiannis DP, Kantarjian H, Elting L, Robertson LE, Keating M. Listeriosis in patients with chronic lymphocytic leukemia who were treated with fludarabine and prednisone. *Ann Intern Med*. 1992;117:466–9.
- Sarrazin JL, Bonneville F, Martin-Blondel G. Brain infections. *Diagn Interv Imaging*. 2012;93:473–90.
- Mylonakis E, Hohmann EL, Calderwood SB. Central nervous system infection with *Listeria monocytogenes*. 33 years' experience at a general hospital and review of 776 episodes from the literature. *Medicine (Baltimore)*. 1998;77:313–36.
- Elzière C, Alkhalil A, Belin C, Dumas JL, Salama JZ. *Listeria monocytogenes* encephalitis revealed by left progressive hemiparesis. *Rev Neurol (Paris)*. 2007;163:592–5.
- Cunha BA, Fatehpuria R, Eisenstein LE. *Listeria monocytogenes* encephalitis mimicking Herpes Simplex virus encephalitis: the differential diagnostic importance of cerebrospinal fluid lactic acid levels. *Heart Lung*. 2007;36:226–31.
- Brouwer MC, van de Beek D, Heckenberg SG, Spanjaard L, de Gans J. Community-acquired *Listeria monocytogenes* meningitis in adults. *Clin Infect Dis*. 2006;43:1233–8.
- Dorta-Contreras AJ. Diagnóstico neuroinmunológico del síndrome de Guillain-Barré. *Rev Neurol*. 2006;43:640. <http://www.neurologia.com/sec/resumen.php?or=web&i=e&id=2006407>. Accessed May 1, 2013.
- Dorta-Contreras AJ, Reiber H. Hallazgos neuroinmunológicos en el diagnóstico de neurotuberculosis. *Rev Neurol*. 2006;43:765–6. <http://www.revneurol.com/sec/resumen.php?id=2006571>. Accessed May 1, 2013.
- Dorta-Contreras AJ, Padilla-Docal B, Coifu-Fanego RB. Using reibergrams to evaluate the intrathecal synthesis of C3c and C4 in children affected with *Neisseria meningitidis* meningoenkephalitis. *Biotechnol Appl*. 2011;28:24–7. http://scielo.sld.cu/scielo.php?pid=S1027-28522011000100004&script=sci_arttext. Accessed May 1, 2013.
- Padilla-Docal B, Iglesias-González I, Bu-Coifu-Fanego R, Socarrás-Hernández CA, Dorta-Contreras AJ. Intrathecal activation as a typical immune response within the central nervous system in angiostrongyliasis. *Am J Trop Med Hyg*. 2013;88:230–5.

23. Just M, Higer HP, Krämer G, et al. Magnetic resonance imaging in infections of the brain: findings in tuberculosis, listeriosis, toxoplasmosis, subacute sclerosing panencephalitis, and multiple sclerosis. *Neurosurg Rev.* 1987;10:185–90.
24. Clauss HE, Lorber B. Central nervous system infection with *Listeria monocytogenes*. *Curr Infect Dis Rep.* 2008;10:300–6.
25. Grumbach NM, Mylonakis E, Wing EJ. Development of listerial meningitis during ciprofloxacin treatment. *Clin Infect Dis.* 1999;29:1340–1.
26. Viale P, Furlanut M, Cristini F. Major role of levofloxacin in the treatment of a case of *Listeria monocytogenes* meningitis. *Diagn Microbiol Infect Dis.* 2007;58:137–9.
27. Leiti O, Gross JW, Tuazon CU. Treatment of brain abscess caused by *Listeria monocytogenes* in a patient with allergy to penicillin and trimethoprim-sulfamethoxazole. *Clin Infect Dis.* 2005;40:907–8.
28. Armstrong RW, Fung PC. Brainstem encephalitis (rhombencephalitis) due to *Listeria monocytogenes*: case report and review. *Clin Infect Dis.* 1993;16:689–702.
29. Büla CJ, Bille J, Glauser MP. An epidemic of food-borne listeriosis in western Switzerland: description of 57 cases involving adults. *Clin Infect Dis.* 1995;20:66–72.
30. Eckburg PB, Montoya JG, Vosti KL. Brain abscess due to *Listeria monocytogenes*: five cases and a review of the literature. *Medicine (Baltimore).* 2001;80:223–35.