CASE REPORT

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Listeria monocytogenes multifocal cerebritis in an immunocompetent adult

Listeria monocytogenes multifokalni cerebritis kod imunokompetentnog bolesnika

Branko Milošević*†, Aleksandar Urošević*†, Nataša Nikolić*†, Ivana Milošević*†, Jasmina Poluga*†, Tanja Tošić‡, Milica Jovanović‡

University of Belgrade, *Faculty of Medicine, Belgrade, Serbia; Clinical Center of Serbia, †Clinic for Infectious and Tropical Diseases, ‡Department of Microbiology, Belgrade, Serbia

Abstract

Introduction. Multifocal cerebritis is a rare and severe disease and just a several cases caused by *Listeria monocytogenes* were described in the literature. **Case report.** A 64 year old man was admitted to the hospital with disturbed consciounsness (Glasgow Coma Scale score: 9) after being febrile for 16 days with history of fever, headache and middle ear pain. He did not have any other comorbidities neither he was immunocompromised. Penicillin allergy was noted for him. On neurologic exam, meningeal or focal neurologic signs were not evident, but computed tomography (CT) brain scan with contrast injection showed 3 hypodense zones in the occipital and 1 in the right temporal lobe. Laboratory findings in blood and cerebrospinal fluid (CSF) were indicative for the infectious nature of changes in the endocranium (multifocal cerebritis). Initial therapy was the combination of cefotaxime, amikacin and metronidazole, but after the isolation of *L. monocytogenes* from CSF and blood culture, therapy was switched to co-trimoxazole. Recovery of consciouscness with establisment of alert state occurred after 6 days of co-trimoxazole administration. Total therapy took 36 days. During that period all clinical and laboratory parameters normalized. The patient was discharged as recovered, with sequelas of amnesia and slurring of speech. **Conclusion.** In the treatment of multifocal cerebritis caused by *L. monocytogenes,* adequate choice and long-term therapy with antibiotics are necessary. The drug of choice is ampicillin but in the case of allergy to it, co-trimoxazole is a good replacement.

Key words:
meningitis, listeria; listeriosis; anti-infective agents; drug combinations; tomography; trimetoprim, sulfamethoxazole drug combination.

Apstrakt

Uvod. Multifokalni cerebritis koji uzrokuje *Listeria monocytogenes* je retko i teško oboljenje koje je u literaturi opisano samo u nekoliko slučajeva. **Prikaz bolesnika.** Bolesnik star 64 godine primljen je u bolnicu poremećene svesti (*Glasgow Coma Scale* skor: 9) nakon 16 dana prethodne febrilnosti, glavobolje i bola u desnom uvu. Nije imao drugih prethodnih bolesti, niti je bio imunokompromitovan. Dobijen je podatak o alergiji na penicilin. Pri neurološkom pregledu nisu evidentirani meningealni znaci i fokalni neurološki poremećaji, a snimak endokranijuma kompjuterizovanom tomografijom sa kontrastom pokazao je tri hipodenzne zone u okcipitalnom i jednu u desnom temporalnom lobusu. Laboratorijski nalazi u krvi i cerebrospinalnoj tečnosti upućivali su na infektivnu prirodu promena u endokranijumu (multifokalni cerebritis). Incijalna terapija bila je kombinacija cefotaksima, amikacina i metronidazola, a nakon izolacije *L. monocytogenes* u kulturi cerebrospinalne tečnosti i hemokulturi, terapija je zamenjena ko-trimoksazolom. Oporavak stanja svesti sa uspostavljanjem budno-svesnog stanja nastupio je nakon šest dana od primene ko-trimoksazola. Ukupno trajanje terapije ko-trimoksazolom iznosilo je 36 dana. U tom periodu normalizovali su se svi klinički i laboratorijski parametri. Bolesnik je otpušten kao oporavljen, sa sekvelama amnezije i usporenog govora. **Zaključak.** U lečenju multifokalnog cerebritisa uzrokovanog *L. monocytogenes* neophodan je adekvatan izbor i dugotrajna primena antibiotske terapije. Lek izbora je ampicilin, ali u slučaju alergije na njega, ko-trimoksazol predstavlja dobru zamenu.

Ključne reči:
meningitis, listeria; infekcija, listerija; antibiotici, kombinovani; kotrimoksazol; tomografija

Correspondence to: Milica Jovanović, Clinical Center of Serbia, Depatment of Microbiology, Bulevar oslobođenja 16, 11 000 Belgrade, Serbia. E-mail: mijovan@eunet.rs

Introduction

Listeria monocytogenes is an important bacterial agent which affects patients with immunosuppression. The most common manifestation of listeria infection involving the central nervous system (CNS) is meningoencephalitis; other less common manifestations include rhomboencephalitis, *ie* brainstem encephalitis (encephalitis of the pons and medulla), and cerebritis with abscess in the absence of meningitis [1]. Brain abscess, recorded in about 1% of affected by this bacterium [1] is a focal form of the infection which usually begins as cerebritis. Multifocal cerebritis is a rare and severe disease and just a several cases caused by *L. monocytogenes* were described in the literature [2–5].

Listeriosis can be a deadly disease: when CNS is involved, fatality rate is 36% [6]; for neurolisteriosis in blood-culture positive patients, mortality is significantly higher [7]. Even when the listeria neuroinfection resolves, sequelae can persist, ranging from neurologic to psychiatric. Psychiatric sequelae can be episodic attacks of stupor or semi-stupor, psycho-organic syndrome, and loss of intellectual abilities with difficulty in concentration and a generalised apathy [8–10].

L. monocytogenes is sensitive to a wide range of antibiotics, but resistant to third generation cephalosporins, usually given as the first line antibiotics when bacterial infections of CNS are suspected. That is why the role of microbiology laboratory is to warn the clinicians about the specificities of the antimicrobial susceptibility of the pathogen as soon as possible, thus increasing the possibility of patient's survival and better recovery. We present the case of the *L. monocytogenes* multifocal cerebritis treated with co-trimoxazole, without surgical intervention.

Case report

A 64 year old man was admitted to the Intensive Care Unit of the Clinic for Infectious and Tropical Diseases of the Clinical Center of Serbia in Belgrade, with disturbed consciousness (Glasgow Coma Scale score: 9) with 16-day history of mild fever (38 °C), headache and infection of the right middle ear, although the discharge from the ear could not be obtained. He did not take antibiotics. His medical history before that was unremarkable, with no immunosuppressive diseases or alcoholism. Penicillin allergy was noted for him. Upon physical examination, he had a body temperature of 38.2 °C and the meningeal signs were not present. Neurologic examination did not show any focal signs, but the computed tomography (CT) brain scan with contrast injection showed three hypodense zones in the occipital and one in the right temporal lobe (Figure 1). Because of febrile condition and disturbed consciousness, neuroinfection was highly suspected (multifocal cerebritis) and decision of lumbar puncture was made. Obtained cerebrospinal fluid (CSF) was opalescent, containing 520 cellular elements, 80:20 ratio of polymorphonuclear leucocytes and lymphocytes, glucose 0.7 mmol/L (blood glucose 5.7 mmol/L), proteins 1.61 g/L, CRP 9 mg/L. Laboratory data from blood showed the following results: erythrocyte sedimentation rate 70 mm/h, neutrophils 21.4 × 10^9, fibrinogen: 6.9 g/L, CRP: 45 mg/L. CSF and blood samples were immediately sent for culture. Initial empirical antimicrobial therapy for multifocal cerebritis with cefotaxime, amikacin and metronidazole was prescribed.

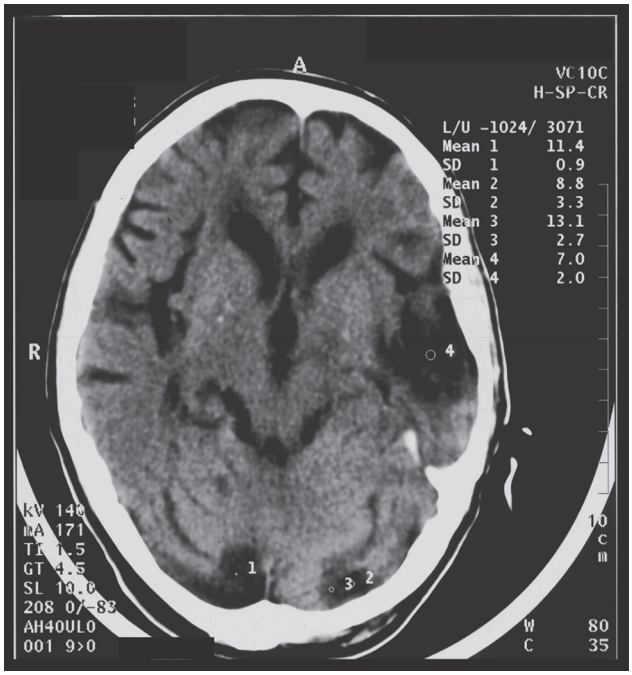

Fig. 1 – Patient's computed tomography (CT) brain scan on presentation; 4 foci visible marked 1, 2, 3 and 4.

The first results from the laboratory revealed rare neutrophils in direct smear of CSF. The next day sparse gray colonies grew on blood agar and they appeared as Gram positive rods on Gram stain, catalase positive and capable of esculin hydrolysis. API *Listeria* system (bioMerieux, Marcy-l'Etoile, France) was set up immediately: the next day it revealed *L. monocytogenes*, code: 6510. The same agent grew from blood culture. The strain was susceptible to penicillin, ampicillin, gentamicin, vancomycin, meropenem, erythromycin, rifampicin and co-trimoxazole when tested by disc diffusion method. On the third day of the patient's stay at the hospital, the antibiotic therapy was switched to co-trimoxazole (20 mg/kg based on trimethoprim component, divided in 4 doses, in a total daily dose of 1,600 mg).

The improvement occurred after 6 days, when his mental status has improved and gradually it became normal (Glasgow Coma Scale score: 15); headache disappeared, as well as fever and pain in the middle ear. Therapy with co-trimoxazole took 36 days in total. At the end of the therapy all parameters of inflammation were in normal range: in blood – erythrocyte sedimentation rate was 18 mm/h, leukocites 6.7 × 10^7, fibrinogen 3.7 g/L, CRP 6 mg/L, and in CSF – 3 cellular elements (lymphocites), glucose 2.9 mmol/L (blood glucose 5.2 mmol/L), proteins 0.49 g/L, CRP < 0.5 mg/L. Control bacterial cultures of blood and CSF were sterile. The patient refused control CT imaging because of the fear of irradiation. After getting satisfactory results, he was discharged, but sequelae persisted. They were of psychic nature – he complained of mild amnesia and slurring of speech.

Discussion

Listeriosis is often associated with certain serious illnesses, namely haematological malignancies or cirrhoses or other immunosuppressive comorbidities [7], presenting as opportunistic infection in diseases where cellular immunity is already impaired. In presenting case, the only disorder the patient suffered from before he lost consciousness was middle ear infection, fever and headache of the duration of 16 days. The data lead to the presumption that middle ear infection can be the source, but we could not find any report about *L. monocytogenes* as a causative agent of that infection in adults, so the theory of contiguous focus of infection from that part of the body, although frequently proven for brain abscess of other etiologies [11, 12], most likely could not be in this case.

The second route of infection like cerebritis is intraaxonal. *L. monocytogenes* can invade the brain tissue by migrating along cranial nerves: V, VII, IX, X, and XII, all of them innervating the oropharynx [13]. It can be speculated that in the present case the bacterium gained entrance to cranial nerves from oropharynx, spread within them and consequently invaded the brain tissue since it was capable of retrograde intra-axonal migration [13]. The ability of *L. monocytogenes* to invade cells, including endothelium of cerebral capillaries in CNS, may favored its spread from CNS to the rest of the body [14], the reason why microorganisms were recovered from blood culture, in addition to the culture of CSF. Corroboration of that thesis is experiment with a rat model of brain abscess caused by *L. monocytogenes* when infectious agent was uniformly present in the circulation of infected rats despite the intracisternal route of infection [14]. Bacteremia is an important feature in human cases of cerebritis due to *L. monocytogenes* [12], while generally in brain abscesses, the report yield of blood cultures is modest, 14%–50% [15].

The third pathogenetic mechanism of the infection in the present case lies in fact that *Listeria* typically enters the body through the gastrointestinal tract, after ingestion the contaminated food. This is the most probable mechanism of development of multifocal cerebritis in the present case. In infected hosts, the bacteria colonize the gut, cross the intestinal wall at Peyer's patches to invade the mesenteric lymph nodes and *via* the lymphatic circulation access the blood. Bacteria are continuously removed from blood by the reticuloendothelial system, but once they become sequestrated in the liver and spleen, they multiply in intracellular sites, including resident macrophages and hepatocytes. Early recruitment of polymorphonuclear cells lead to hepatocyte lysis, creating necrotic foci and thereby bacterial release in the circulation. This causes prolonged septicaemia, thus exposing the brain to infection [16]. Bone marrow has a key function in that process: a specific subset of its monocytes, marked Ly-6ChighCD11bpos, are recruited to transport *Listeria* from the bone marrow to bloodstream and from there into the brain [17].

L. monocytogenes gains access to the brain parenchyma via the cerebral capillary endothelium, a single layer of specialized human brain microvascular endothelial cells characterized by tight junctions. *L. monocytogenes*-infected monocytes can penetrate these endothelial cells via the middle cerebral artery resulting in cerebritis and, subsequently, brain abscess formation [1]. It seems that in the pathogenesis of neuroinfection caused by *L. monocytogenes*, persistent bacteremia is necessary [18] and it has been confirmed by the studies of Cone et al. [1] or Dee and Lorber [12], who reviewed three and eight cases of multiple cerebral abscess, respectively. In all of them, the etiologic agent was isolated from blood culture, like in the present case report, and in our patient it was probably manifested by mild fever and headache.

Fever, altered sensorium and headache are the most common symptoms of CNS listeriosis, but 42% of patients do not have meningeal signs on admission. Compared with patients with acute meningitis due to other bacterial pathogens, patients with *Listeria* infection had a significantly lower incidence of meningeal signs, and so it was with our patient. Lumbar puncture was performed on the admission because the patient had disturbance of consciousness, fiver and laboratory findings which implied neuroinfection.

Patients with brain abscess, encephalitis, or rhombencephalitis should be treated for at least 6 weeks and this is the reason for duration of therapy of 36 days. The combination of ampicillin with gentamicin is generally recommended as a first-line therapy for the treatment of listeriosis in humans [19, 20]. Studies *in vitro* or on animal models show the higher activity of penicillin antibiotics (ampicillin or amoxicillin) or combination of penicillin and aminoglycoside antibiotic, or quinolones [14, 21] than co-trimoxazole,although the last antibiotic penetrates the cell wall well and has bactericidal activity. In cases of penicillin hypersensitivity, co-trimoxazole is the treatment of choice.

There are scarce data in the literature about the usage of co-trimoxazole in invasive human listeria infections, but according to some case reports it seems to have a good effect [22–25]. A retrospective study of 22 cases of listeria meningoencephalitis even demonstrated superiority of that antibiotic combined with ampicillin over gentamicin with ampicillin [26]. Cephalosporins have limited activity against listeria. Vancomycin has poor penetration into the central nervous system due to its hydrophilic nature and high molecular weigh [27]. Although meropenem has better *in vitro* activity then ampicillin, clinical data are not conclusive and failure after treatment was suspected on the basis of case-reports [28].

This report is a confirmation of the efficacy of co-trimoxazole in the conservative treatment of severe disease such as listeria multifocal cerebritis with bacteremia. Amnesia and slurring of speech can appear insignificant in the absence of more severe psychiatric syndromes and highly lethal disease.

Conclusion

Multifocal cerebritis due to *L. monocytogenes* in immunocompetent patients is rare diseases. Co-trimoxasole as somewhat neglected antibiotic showed good efficiency as alternative choice in the patient allergic to penicillin. This case showed that a severe CNS infection can be cured by sufficiently long therapy with co-trimoxazole.

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