



Case Report

Pseudomonas aeruginosa nosocomial meningitis following spinal anesthesia – still a significant treatment dilemma

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Received : 02 July 2022

Accepted : 19 August 2022

Published : 02 September 2022

DOI

10.25259/SNI_594_2022

Quick Response Code:



ABSTRACT

Background: Infections of central nervous system after spinal anesthesia nowadays are a rarity; however, their presence might be of concern.

Case Description: We report the case of lateral ventricular empyema treated unsuccessfully with parenteral antibiotic therapy, with the clinical signs of a persisting meningitis. After several lumbar taps suggesting an infection, *Pseudomonas aeruginosa* was isolated and a brain magnetic resonance imaging find out the collection in the left horn of the lateral ventricle. An intrathecal/intraventricular antibiotic therapy with colistin proved highly effective combined with an extra ventricular drainage to deal with the hydrocephaly.

Conclusion: Clinicians should take into account even uncommon infectious agents while facing the picture of a meningitis otherwise nonresponsive to empiric or standard therapy.

Keywords: Brain magnetic resonance imaging, Meningitis, *Pseudomonas aeruginosa*, Spinal anesthesia, Ventricular empyema

INTRODUCTION

Infections of the central nervous system (CNS) due to *Pseudomonas aeruginosa* are uncommon and nosocomial meningitis from a not careful asepsis especially after spinal anesthesia is even rarer. Infections enter into the cerebrospinal fluid (CSF) through two main routes. The first relates to the inobservance of aseptic techniques, which lets the external infectious agents enter the CSF. The second comes when the bacteria in the patient's blood at the time of lumbar puncture (LP) access the subarachnoid space due to the microscopic bleeding caused by the insertion of the needle.^[10]

According to several retrospective studies, the incidence of infectious complications after epidural and spinal anesthesia varies from 0% to 0.04%^[9] *P. aeruginosa* meningitis is more common with intraventricular (IVT) catheters and is associated with high mortality.^[12] *Pseudomonas* meningitis is a severe nosocomial meningitis associated with reported mortality of 21–40% that occurs predominantly secondary to invasive procedures.^[11]

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Diagnosing and adequately treating infections from *P. aeruginosa* are therefore important, while facing Gram-negative pathogens, due to the increasing antimicrobial resistance in the health-care setting.^[25] The treatment of this entity is difficult since antimicrobial treatment of CNS infections relies not only on the susceptibility of the isolated microorganism but also on the treatment's pharmacokinetic properties of the drug.

The treatment of *P. aeruginosa* meningitis poses a severe challenge due to the scarce number of drugs available for its treatment. The poor diffusion of most of the antimicrobial agents into the CNS through the brain-blood barrier (BBB) is another issue.

Conventionally, some drugs, such as cephalosporins, quinolones, carbapenems, colistin, or aminoglycosides (the two latter used also intrathecal [IT]), have been used for the treatment of meningitis caused by *P. aeruginosa*.^[8] IT antibiotics in these CNS infections are rarely applied. While facing antibiotic-resistant organisms or treatment failures, this route can be successful.^[22]

Here, we present a case of *P. aeruginosa* meningitis in a 26-year-old woman following spinal anesthesia for cesarean section, its clinical characteristics, and treatment challenges.

CASE PRESENTATION

A 26-year-old woman was hospitalized 1 week after a cesarean delivery under spinal anesthesia, due to high fever and persistent headache. She received at home a treatment with intravenous ceftriaxone for 4 days. With no signs of clinical improvement, the woman was admitted in our Infectious Diseases Clinic at the University Hospital Center with the suspected diagnosis of bacterial meningitis.

The patient was previously healthy, and her immunological status was considered competent. On admission, the HIV serology was negative; and no history of any important medical condition was reported.

A LP performed immediately in the emergency room, which determined the pleocytosis and the diagnosis of an acute bacterial meningitis. Leukocyte cells count was 723 cells/ μ L with 94% segmented neutrophils, CSF glucose was very low, and protein was 420 mg/dl. *P. aeruginosa* was isolated from CSF culture and it was sensitive to all antibiotics of standard panel. The cranial and lumbar region computerized tomography scan resulted normal, with no image for intraspinal or epidural abscesses or vertebral osteomyelitis. Blood cultures resulted negative.

We modified the empiric treatment with intravenous ceftriaxone to ceftazidime and gentamycin for 2 weeks. Fever and headache were resolved 5 days after the beginning of treatment, and she left the facility. 3 days after discharge, she reported high fever and strong headache and came back to hospital.

The length of hospital staying for this second time was one month. We performed again a lumbar tap on admission and had a count of white blood cells (WBC) of 850 cells/ μ L (86% were segmented neutrophils), glucose of 18 mg/dl (blood glucose 112 mg/dl) and protein was 450 mg/dl. We restarted treatment with ceftazidime and amikacin, while CSF culture grew once again ceftazidime sensitive *P. aeruginosa*.

We repeated LP 2 weeks later, due to fever and strong headache and we found out that WBC of CSF were 180 cells/ μ L, polymorphs were 93%, and glucose was low and protein high again. We stopped amikacin and switched antibiotic treatment to ceftazidime, Imipenem, and levofloxacin. There was no headache improvement, and the fever was fluctuating 38–39°C.

Cranial and lumbar magnetic resonance imaging (MRI) and cardiac ultrasonography resulted normal, so we repeated LP, and this time, we counted 320 WBC/ μ L, and *P. aeruginosa* was isolated from CSF culture. Intravenous colistin replaced levofloxacin and 10 days after her headache worsened and the patient had a generalized seizure. The repeated cranial MRI showed hydrocephaly and IVT empyema in the occipital horn of the left lateral ventricle [Figure 1].

An extra ventricular drainage helped to resolve hydrocephaly, and we applied IVT colistin for 14 days with a dose of 125,000 IU (10 mg). On the 6th day after the initiation of this treatment, the patient's clinical condition improved and CSF culture resulted negative. One month after discharge, she was in a very good condition and neurosurgeons inserted a ventricular-peritoneal shunt. In the follow-up 6 months later, the patient remained free of the symptoms. A control MRI [Figure 2] demonstrated as well the resolution of the ventricular empyema.

DISCUSSION

This case report describes clinical and laboratory data, as well as important treatment issues of *P. aeruginosa* meningitis

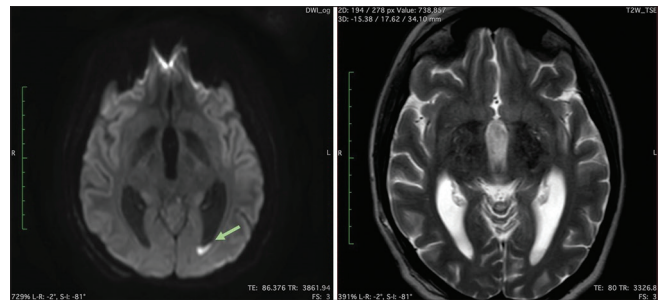


Figure 1: Non-enhanced brain magnetic resonance imaging. Left inset: imaging suggested an intraventricular empyema (pyogenic ventriculitis) in the occipital horn of the left lateral ventricle, visible only in the diffusion-weighted image (arrow). Right inset: the collection is invisible in the T2-weighted image. There is a notable ventricular enlargement.

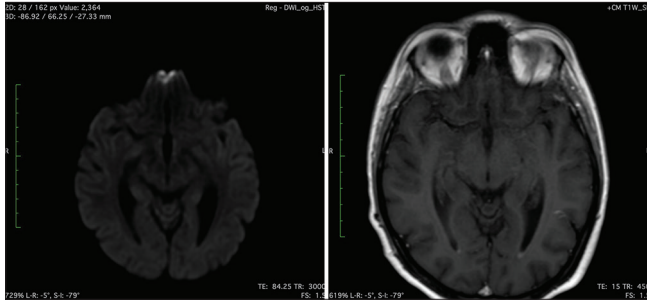


Figure 2: Non-enhanced brain magnetic resonance imaging: follow-up 3 weeks after the intrathecal antibiotic therapy. The collection is no longer visible both in the diffusion-weighted image (left inset) as well as the in the T1-weighted image in (right inset). The hydrocephaly although still present, is slightly improved.

following spinal anesthesia. Reports of *P. aeruginosa* meningitis after spinal anesthesia are rare, especially after careful standard asepsis that should accompany LPs. However, we should consider that the LP (for whatever purposes) bypasses all the natural defense barriers of the CNS, and it is therefore clear that it carries at least the theoretical risk of introducing infection and causing meningitis.^[3]

In our case, it was impossible to find out why the procedure, normally performed under strict aseptic conditions, and was associated with this kind of infection. Immediately after CSF culture, where *P. aeruginosa* was isolated, we adopted antimicrobial therapy to antibiotics that have a good penetration through BBB and an adequate antimicrobial coverage as anti-*Pseudomonas* and prescribed their optimal dosing for sites such meninges. Nevertheless, the clinical outcome was suboptimal.

The two key factors influencing antimicrobial treatment of CNS infections relate to the susceptibility of the isolated microorganism as well as the pharmacokinetic properties of the antimicrobial molecule to penetrate the BBB. The choice and kinetics of antimicrobials in CNS infections are of utmost importance and the BBB has specific features that limit the passage of molecules on several parameters such as size, lipophilia, and plasma protein binding along with transporter affinity.^[18]

The treatment of *P. aeruginosa* meningitis relies on the general principles of bacterial meningitis treatment, that is, the prompt diagnosis of the infection and early effective antimicrobial therapy. Third-generation cephalosporins have been widely used in the treatment of patients with Gram-negative bacillary meningitis over the past 20 years, because these antibiotics penetrate well into the CSF after intravenous administration and this has resulted in dramatic decreases in meningitis-related mortality.^[17]

The first systemic treatment of our patient lasted 21 days with ceftriaxone as an empiric therapy at the beginning, and

ceftazidime combined with gentamycin following, when results showed positive CSF cultures for *P. aeruginosa*. Recommended duration of therapy ranges from 14 to 28 days.^[13] Although current data suggest that ceftazidime is the antibiotic of choice for *P. aeruginosa* meningitis, we experienced treatment failure, and several reasons might have contributed.^[7]

One of them relates to the antibiotic penetration and low CSF concentrations. Studies have shown that in patients with acute bacterial meningitis the CNS transfer of drugs increases, due to the opening of intracellular tight junctions, increased CSF outflow resistance, a low pH and by transporters' stimulation by pro-inflammatory cytokines. The treatment of *P. aeruginosa* meningitis poses a severe challenge due to the scarce number of drugs available for its treatment and also for the poor diffusion of most of the antimicrobial agents into the CNS through the BBB.^[8]

Another explanation for the high relapse rate might be that *P. aeruginosa* produces robust biofilms.^[23] Both treatment failure and relapses might occur, and the recorded mortality is often high, approaching 80% in some studies.^[15] Besides, we think that complications such as pyogenic ventriculitis (synonymous to pyoventriculitis) and hydrocephaly that occurred in our case were related to intravenous antibiotic treatment failures.^[1] Therefore, we considered the use of IVT antibiotics after external ventricular drain, in combination with intravenous antibiotics. IVT antibiotics ensure a high concentration of antibiotic at the site of infection, bypassing BBB. There are reports of IVT antibiotic therapy dating more than 17 years from now.^[4]

The Infectious Diseases Society of America guidelines recommended IT/IVT therapy daily dose of 10 mg of colistimethate sodium (CMS) (about 125 000 IU CMS, equivalent to 3.75 mg colistin base activity).^[5,20] The major reason for the cautioned use of IVT/IT therapy has been the significant toxicity reported by earlier studies. These included seizures in up to 20% of the patients and chemical ventriculitis in as high as 60% of the patients, though these were mostly dose-related.^[16] Few papers have also reported side effects such as transient hearing loss and seizures while using gentamicin and vancomycin. Most recent studies have shown little or no serious adverse effects with the use of polymyxin B, colistin, and vancomycin, making them the most commonly used IVT agents.^[2,21]

In collaboration with neurosurgeons, an extra ventricular drainage helped our case to resolve hydrocephaly and IVT colistin was injected until the last examination of CSF taken from the external drainage resulted negative for WBC and the culture showed no *P. aeruginosa* growth (on the 6th day of local treatment). We used IVT colistin for 14 days with a dose of 125,000 IU (10 mg) as the only alternative treatment option together with the systemic antimicrobial treatment. We had

no side effects while applying IVT therapy. After 1 month, she was in a very good condition and a ventriculoperitoneal shunt was in place. Our patient remained free of symptoms for a 6 months follow-up from the day, she left the hospital.

The few data available on the pharmacokinetics of polymyxins in CSF report a low diffusion through the CNS, with unclear rate of penetration and a possible role for meningeal inflammation. Colistin penetration in the CNS, even when meninges are inflamed, is poor, and its concentration in CSF reaches approximately 10% of its concentration in serum.^[14] According to these studies, intravenous colistin alone does not provide CSF concentrations high enough to reach a MIC of two mcg/mL for multidrug resistance Gram-negative rods, and therefore, there is a need for topical administration to achieve best results.

On this basis, alternative therapeutic strategies may be necessary and the IT use of colistin is available as an adjuvant therapy to intravenous administration for infection.^[6] The mean period to sterilize the CSF after appropriate IVT antibiotic treatment is 6.6 days.^[24] The previous studies have reported that treatment with intravenous and IT colistin with a wide dosing range from 1.6 to 40 mg (20,000–500,000 IU) may be associated with excellent cure rates. However, reports of deaths and complications such as chemical meningitis are available, although in small series.^[19]

CONCLUSION

P. aeruginosa meningitis after spinal anesthesia is a nosocomial infection and clinicians can often experience systemic antibiotic treatment failures even when this treatment consists in broad-spectrum anti-pseudomonal agents based on culture results. Even after an early microbiologic diagnosis and an appropriate choice of antibiotics, based on bacterial meningitis treatment criteria and antibiogram, eradication of the bacteria from CSF is difficult. IVT antibiotic use for *P. aeruginosa* meningitis is a good treatment option, although some studies have raised controversies. To eradicate this nosocomial infection, sources suggest a prolonged intravenous antibiotic course, combined with local treatment. More aggressive interventions and earlier IVT/IT therapy application for *P. aeruginosa* meningitis will enhance the success rates of the treatment.

Declaration of patient consent

Patient's consent not required as patient's identity is not disclosed or compromised.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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How to cite this article: Kolovani E, Ramosaço E, Xhumari A, Vyshka G, Ranxa E. *Pseudomonas aeruginosa* nosocomial meningitis following spinal anesthesia – still a significant treatment dilemma. Surg Neurol Int 2022;13:400.