ISSN: 2474-9206

Case Report

Journal of Anesthesia & Pain Medicine

Disseminated Mycobacterium Tuberculosis Infection with Central Nervous System Involvement and Ponchet's Disease

Stamatis Karakonstantis*[1], Sofia Pitsigavdaki[1], Dafni Korela[1], Athina Savva[2], Evgenia Emmanouilidou[1], Despoina Galani[1], Melina Kavousanaki[1], Thalassinos Evangelos[1] and Charalampos Lydakis[1]

[1]*2nd Department of Internal Medicine, General Hospital of Heraklion "Venizeleio-Pananeio", Heraklion, Crete, Greece*

[2]*Radiology Department, General Hospital of Heraklion "Venizeleio-Pananeio", Heraklion, Crete, Greece*

***Corresponding author**

Stamatis Karakonstantis, Department of Internal Medicine, General Hospital of Heraklion "Venizeleio-Pananeio", Heraklion, Crete, Greece, Tel: +30-6940100298; E-mail: stamkar2003@gmail.com.

Submitted: 09 Apr 2018; **Accepted**: 18 Apr 2018; **Published**: 24 Apr 2018

Abstract

Background: *Diagnosing central nervous system (CNS) tuberculosis is challenging because of its rarity, indolent course, and insensitive microbiological diagnosis. The mortality of the disease is high even with prompt initiation of appropriate therapy.*

Case report: *A 36-year-old male from Pakistan with no past medical history was brought to the hospital with fever (39°C) and altered behavior since 2 weeks. He was confused, with nuchal rigidity, an enlarged right cervical lymph node and swelling of the left knee and ankle. The first brain CT was normal. Lumbar puncture revealed lymphocytic pleocytosis with elevated protein and low glucose. He was started on ceftriaxone, ampicillin and acyclovir pending further cerebrospinal fluid (CSF) analysis. CSF acid-fast staining, tuberculin skin test, CSF PCR for mycobacterium tuberculosis, testing for HIV, Cryptococcus and syphilis were all negative. Due to the patient's worsening neurological status, a brain MRI was performed revealing worsening hydrocephalus, leptomeningeal enhancement and brain edema, findings consistent with tuberculous central nervous system infection. A ventriculostomy was placed and he was started on anti-tuberculosis therapy and adjunctive prednisone. The diagnosis of tuberculosis was later confirmed from culture of the CSF. Synovial fluid analysis revealed 30 leukocytes/ul, with negative cultures (suggesting Poncet's disease). Despite improvement of the level of conscience, neurological improvement was otherwise limited, and the patient died 4 months later after repeated in-hospital infections.*

Discussion: *Considering the morbidity and mortality of CNS tuberculosis empirical initiation of therapy is important when the clinical suspicion is high.*

Keywords: Tuberculosis, Meningitis, Central Nervous System, Arthritis, Ponchet

Introduction

The global burden of tuberculosis is significant [1]. According to the latest WHO global tuberculosis report more than 10 million people fell ill with tuberculosis in 2016, and 1.8 million died from tuberculosis. Extrapulmonary tuberculosis represents about 15% of these cases. Central nervous system involvement, although rare, is the most devastating complication, associated with a very high mortality (up to 50% in HIV co-infected patients) [1]. However, the diagnosis is often delayed, as both acid-fast stain and molecular techniques for detection of tuberculosis in the CSF are insensitive.

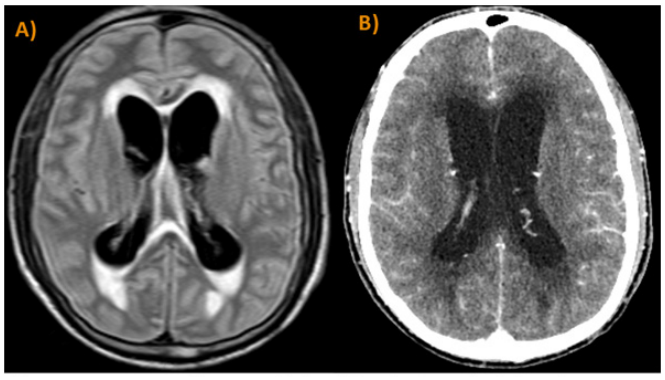
Case report

A 36-year-old male from Pakistan was brought to the hospital with fever (39°C) and altered behavior since 2 weeks. His past medical history was unknown. He appeared malnourished and was confused and disoriented. He was febrile (39°C), with a blood pressure of 100/60mmHg and tachycardic (110 beats per minute). The physical examination was positive for nuchal rigidity, and an enlarged right cervical lymph node was noted, as well as painful knee and ankle joints. The initial laboratory tests (complete blood count and blood chemistry) were non-specific (low inflammatory markers and lymphocytopenia). A head computed tomography (CT) was performed in the Emergency Department and was normal. A lumbar puncture for cerebrospinal fluid (CSF) analysis was then performed revealing lymphocytic pleocytosis, elevated protein and low glucose (500 leucocytes, 83% lymphocytes, protein 314 mg/dL and glucose 32mg/dL). The CSF gram stain was negative. Following the lumbar puncture, he was started on an empirical regimen including ceftriaxone, ampicillin and acyclovir pending further cerebrospinal fluid (CSF) analysis. The chest x-ray and an abdominal ultrasound were normal.

PCR of the CSF for several causative agents of bacterial meningitis (Neisseria meningitis, Streptococcus pneumoniae, Haemophilus influenzae type b, non-type b Hemophilus influenza, Listeria monocytogenes, Streptococcus spp, Pseudomonas aeruginosa, and Staphylococcus aureus) and for herpes simplex viruses were all negative. CSF acid-fast staining and PCR of the CSF for mycobacterium tuberculosis were negative. A tuberculin skin test was also negative (induration "0" cm). India ink staining and testing of the CSF for cryptococcal antigen were both negative. Serology for HIV (using a 4th generation antigen/antibody assay), syphilis (using a treponemal-specific test), Brucella, Bartonella, Leptospira, Toxoplasma, EBV and CMV were also negative. The knee effusion was also aspirated and was analyzed with microcopy, gram stain, acid-fast stain, PCR for mycobacterium tuberculosis and culture. All were negative. The white blood cell count of the effusion was 37.

Due to the patient's worsening neurological status during the first 2 days of hospital stay, an MRI was performed revealing hydrocephalus, cerebral edema and leptomeningeal enhancement, all findings typical of tuberculous meningitis. Therefore, the patients was started on anti-tuberculosis therapy (isoniazid, pyrazinamide, rifampicin, moxifloxacin) and adjunctive prednisone. Despite a transient improvement, the mental status of the patient deteriorated. The patient was admitted to the ICU and a ventriculostomy was placed. During his ICU stay a chest CT revealed infiltrates of the right upper lobe, which were not evident in the admission chest x-ray. A BAL (bronchoalveolar lavage) sample was obtained and the PCR for mycobacterium tuberculosis was positive. However, the neurological improvement of the patient was limited, and the patient died 4 months later after repeated in-hospital infections.

Eventually the diagnosis was confirmed when mycobacterium tuberculosis was isolated from the CSF culture. Antimicrobial susceptibility testing (with PCR and culture) confirmed the susceptibility to all the agents of our treatment regimen. Of note is that of 3 separate lumbar punctures (during the first 3 days of hospital stay) the culture was positive in only one of the samples. Acid-fast stain was negative in all of the samples.



A) Brain MRI, FLAIR sequence, demonstrated hydrocephalus with trans-ependymal edema. B) Post-contrast brain CT demonstrating leptomeningeal enhancement

Discussion

Our case illustrates the low diagnostic yield of microbiological tests in patients with tuberculous CNS infection, which often necessitates empirical initiation of treatment. In our patient the negative acid-fast stain combined with the negative CSF PCR and a normal initial brain CT resulted in inappropriate delay in the initiation of anti-tuberculous therapy. However, both acid-fast stain and CSF PCR have suboptimal sensitivity for the diagnosis of tuberculous CNS infections [1,2]. Some simple measures, like using a high CSF volume and centrifugation of the CSF, may improve the sensitivity of these diagnostic tests [1,3]. Furthermore, using the newer molecular techniques (like Xpert MTB/RIF Ultra, which is currently favored by WHO as the preferred initial test) may further increase the yield of diagnostic testing [1,4].

Our choice to use a fluoroquinolone (moxifloxacine) in place of ethambutol (the typical 4th drug in the first-line anti-tuberculous regimen) was based on the fact that CNS penetration of ethambutol is insufficient [1]. On the contrary, fluoroquinolones like levofloxacin and moxifloxacin, have good CSF penetration [5,6]. However, adding a fluoroquinolone in the treatment regimen has not been proven beneficial so far in clinical trials [7-9]. Nevertheless, in patients with isionazid-resistant mycobacteria, an intensified regimens using a high dose of rifampicin with the addition of levofloxacin as a fifth agent improved survival [8].

The arthritis in our patient probably reflects Poncet's disease [10]. This refers to aseptic arthritis, typically polyarthritis, in patients with mycobacterium tuberculosis. By definition, as in our case, mycobacterium tuberculosis is not isolated from the joint effusion. The arthritis responds well to treatment for tuberculosis.

Conclusion

When the clinical suspicion for tuberculosis with CNS involvement is sufficiently high, treatment should be initiated empirically without awaiting culture results even if other faster tests (like acid-fast stain and PCR) are negative.

References

1. Wilkinson RJ, Rohlwink U, Misra UK, van Crevel R, Mai NTH, et al. (2017) Tuberculous meningitis. Nature Reviews Neurology 13: 581.
2. Denkinger CM, Schumacher SG, Boehme CC, Dendukuri N, Pai M, et al. (2014) Steingart KR. Xpert MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis: a systematic review and meta-analysis. The European respiratory journal44: 435-446.
3. Thwaites GE, Chau TTH, Farrar JJ (2004) Improving the Bacteriological Diagnosis of Tuberculous Meningitis. Journal of clinical microbiology 42: 378-379.
4. Bahr NC, Nuwagira E, Evans EE, Cresswell FV, Bystrom PV, et al. (2018) Diagnostic accuracy of Xpert MTB/RIF Ultra for tuberculous meningitis in HIV-infected adults: a prospective cohort study. The Lancet Infectious diseases 18: 68-75.
5. Thwaites GE, Bhavnani SM, Chau TT, Hammel JP, Torok ME, et al. (2011) Randomized pharmacokinetic and pharmacodynamic comparison of fluoroquinolones for tuberculous meningitis. Antimicrob Agents Chemother 55: 3244-3253.
6. Alffenaar JW, van Altena R, Bokkerink HJ, Luijckx GJ, van Soolingen D, et al. (2009) Aarnoutse RE, et al. Pharmacokinetics of moxifloxacin in cerebrospinal fluid and plasma in patients with tuberculous meningitis. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America 49: 1080-1082.
7. Donald PR (2016) Chemotherapy for Tuberculous Meningitis. New England Journal of Medicine 374: 179-181.

8. Heemskerk AD, Bang ND, Mai NTH, Chau TTH, Phu NH, et al. (2016) Intensified Antituberculosis Therapy in Adults with Tuberculous Meningitis. New England Journal of Medicine 374: 124-34.
9. Ruslami R, Ganiem AR, Dian S, Apriani L, Achmad TH, et al. (2013) Intensified regimen containing rifampicin and moxifloxacin for tuberculous meningitis: an open-label, randomised controlled phase 2 trial. The Lancet Infectious diseases 13: 27-35.
10. Kroot EJ, Hazes JM, Colin EM, Dolhain RJ (2007) Poncet's disease: reactive arthritis accompanying tuberculosis. Two case reports and a review of the literature. Rheumatology 46: 484-489.