Case Report

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Enterobacter Meningitis and Challenges in Treatment

Internal Medicine Section

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ABSTRACT

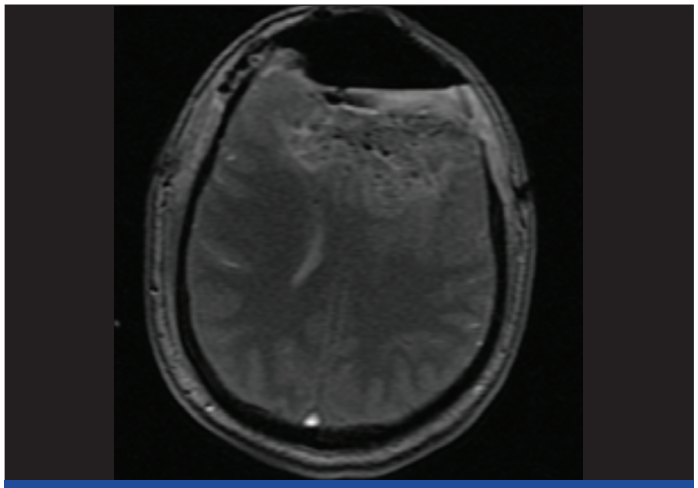
Neurosurgical interventions are rarely associated with meningitis with a very low incidence rate ranging from 1.1% to 2.5%. Gram negative bacillary meningitis first described in the 1940's, previously uncommon has been increasing in the recent past associated with advanced age, immunosuppression and neurosurgery. *Enterobacter* meningitis though relatively uncommon is recently increasing in incidence and treatment is frequently complicated due to resistance to antibiotics making this a challenging, difficult to treat infection that may be associated with adverse clinical outcomes. Here, we describe a case of a 27-year-old patient diagnosed with brain sarcoma at the age of four years, who presented with *Enterobacter* meningitis following a neurosurgical intervention for resection of a recurrent brain tumor (meningioma on pathology) and had a prolonged hospital stay with a difficult to treat infection.

Keywords: Bi-frontal craniotomies, Immunosuppression, Neurosurgical interventions

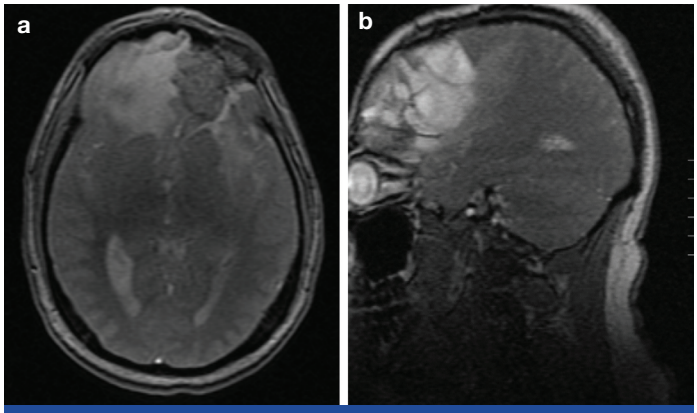
CASE REPORT

A 27-year-old male patient presented to the hospital with intermittent high grade fever and headaches since undergoing bi-frontal craniotomy and resection of brain tumor involving the left frontal lobe extending over the midline and involving the medial aspect of the right frontal lobe in January 2016. He had a long standing history of bi-frontal tumor from the age of four years, reportedly a sarcoma. In 1993, he underwent initial resection of the tumor followed by chemotherapy and bone marrow transplant, with a repeat resection in 1994, followed by stereotactic radiation therapy. He underwent his 3rd resection of a recurrent brain tumor in January 2016 with fever beginning the following day and he had been febrile on a nearly daily basis with occasional spikes up to 102°F since then. His tumor was found to be a meningioma at this time of admission. Patient has tumor-related epilepsy since 2001 with placement of a vagal nerve stimulator in 2009 which has subsequently been removed in January 2016 after infection at the craniotomy site. He also has a history of type II Diabetes Mellitus and Non Alcoholic Steato-Hepatitis (NASH).

On the first post-operative day, patient underwent a Magnetic Resonance Imaging (MRI) which showed post-operative changes from bi-frontal craniotomies and resection of frontal lobe masses. There was no imaging evidence of residual tumor [Table/Fig-1]. White Blood Cell (WBC) count was 14,100/mm^3 and there was no obvious source of infection. Patient was initially treated with Cefepime (2 g i.v every 8 hours) and Vancomycin (1500 mg i.v every 8 hours) which were then stopped due to no obvious source of infection and patient was discharged on post-operative day 5. He was readmitted on post-operative day 7 to post-operative day 13. Computed Tomography (CT) scan done on post-operative day 9 showed bilateral frontal scalp pseudomeningoceles with the appearance indeterminate for superimposed infection. Surgical site was healing well. There was no obvious source of infection. A diagnosis of drug fever due to recently changed anti-epileptic drug was considered in the presence of a negative work-up for an infective source. His fever continued to spike to100.2°F. He was re-admitted on post-operative day 22 with high grade fever and pus at surgical site and on physical examination his heart rate was 104/min, SpO_2 99% on 2 liters, respiratory rate 18/min and temperature was 100.2°F. On neurological examination patient was awake and alert and followed commands appropriately initially treated with meropenem (2 gm i.v q8) and vancomycin (1500 mg i.v every 8 hours). Complete blood count showed hemoglobin 16.5g/dl, WBC 18,500/mm^3, platelet count 318x10^3/ml. MRI done in this admission showed large bi-frontal air fluid abscess involving the bi-frontal encephalomalacia bed and bi-frontal scalp, ventriculitis with layering pus in occipital horn of both lateral ventricles and meningitis [Table/Fig-2a,b]. Lumbar puncture done showed a CSF protein of 934mg/dL, glucose of 46mg/dL, WBC 6,811/µL, RBC 3,950/µL and Xanthochromia was negative. Cerebrospinal Fluid (CSF) cultures grew *Enterobacter aerogenes* sensitive to Trimethoprim/Sulfmethoxazole, Ciprofloxacin, Gentamicin, Piperacillin/Tazobactam, Ceftriaxone and resistant to Cefazolin. Patient underwent frontal lobe craniotomy and wash-out and was started on Gentamicin via intrathecal route, i.v. Cefepime and i.v.



[Table/Fig-1]: Post-operative changes from bi-frontal craniotomies and resection of the previously noted frontal lobe masses. No imaging evidence of residual tumor.



[Table/Fig-2a,b]: Large complex partially calcified cystic and solid mass greater on the left compared to the right consistent with residual/recurrent sarcoma.

Ciprofloxacin. Ciprofloxacin was discontinued on post-operative day 32. Repeat CSF cultures showed no growth and patient was subsequently monitored by CSF studies. He continued to improve for the next 4-5 days when repeat CSF studies show increased leukocytosis along with persistence of fever at which time antibiotics were switched to Meropenem and Vancomycin and CSF drain was removed. Subsequent CSF studies showed decrease in leucocytosis and patient showed clinical improvement and he was transferred from Intensive Care Unit (ICU). During the hospital course, his anti-seizure medications of clobazam (oral 25 mg every day), lacosamide (oral 100 mg dose: 250 mg every evening; lacosamide oral 50 mg dose: 150 mg every day), levetiracetam (oral 750 mg dose: 1500 mg 2 times per day), primidone (oral 250 mg dose: 250 mg at bedtime) and topiramate (400 mg every day) were continued and his Type II DM was managed with insulin.

DISCUSSION

Central nervous system infections are rarely caused by gram negative bacilli but if present they are commonly associated with history of head trauma, neurosurgical interventions and immunocompromised state [1]. *Enterobacter* meningitis first described in the 1940's [1] has seen a recently increasing incidence with unique challenges in treatment due to antibiotic resistance. *Enterobacter* spp., gram negative bacilli, has intrinsic resistance to older antibiotics and has the ability to acquire resistant to newer antibiotics also [2]. *Enterobacter* cloacae and *Enterobacter aerogenes*, part of normal gut flora are the two most frequently isolated pathogens from nosocomial infections capable of causing infections in immunocompromised patients.

Our patient had *Enterobacter* meningitis following a neurosurgical intervention and a difficult to treat infection leading to a prolonged hospital stay and significant morbidity. Similar findings have been described from other studies. Parodi S et al., in their eight-year study, found 15 post-neurosurgical cases of *Enterobacter* meningitis, *E. aerogenes* species, being isolated from CSF samples of 16% of the study population at the University of California–Los Angeles (UCLA) Medical Center [3]. Independent risk factors for nosocomial *Enterobacter* meningitis are *Enterobacter* colonization or infection at a non-CSF site, history of antibiotic drugs, especially broad-spectrum β-lactams, and external CSF drainage catheters [3]. Our patient had these risk factors including prior antibiotic treatment and multiple neurosurgical procedures. A study of 3000 patients showed that patients who had undergone craniotomy, only 2.5% developed brain abscess or meningitis during post-operative period from day 2 to day 18 with average developing on 10th day. They reported that the most common organism was *Staphylococcus aureus*, followed by *Enterobacter* [1]. Disruption of dura-arachnoid barrier either from surgery or trauma may result in nosocomial meningitis commonly caused by *Enterobacter* species [1].

Enterobacter aerogenes, commonly associated with nosocomial infection naturally produces Extended-Spectrum Beta-Lactamase (ESBL), Transmission Electron Microscopy (TEM-24), resulting in resistance to β-lactam antibiotics while some strains have drug efflux pumps making them resistant to β-lactam antibiotics, quinolones, tetracycline and chloramphenicol [4,5]. Cephalosporin-resistant *Enterobacter* meningitis is treated mainly by Trimethoprim-Sulfamethoxazole and Carbapenems [3]. Concern about *Pseudomonas aeruginosa* and other resistant gram-negative organisms has limited the use of Trimethoprim-Sulfamethoxazole to empirical therapy for gram-negative bacillary meningitis in neurosurgical patients though studies have reported that Trimethoprim-Sulfamethoxazole can be used to treat *Enterobacter* infections [6]. Cefepime, intracisternal/intrathecal Gentamicin, Imipenem plus intrathecal Amikacin, Trimethoprim-Sulfamethoxazole plus Gentamicin, and Ciprofloxacin are other antibiotics that can be used in *Enterobacter* meningitis [7]. Our patient required treatment with various broad spectrum antibiotics and a prolonged hospital stay with administration of an extensive antibiotic regimen.

There is no routine indication of CSF culture in patients with external ventricular drains, various indications to perform CSF culture include fever (>38.5°C) or leukocytosis, detoriation in neurological functions, or any change in CSF appearance [8]. Our patient had an external ventricular drain and CSF cultures were repeated due to change in CSF appearance and persistent fever. Patient had a negative CSF culture in two days as seen by Parodi et al., where the median time for sterilization of the CSF was two days [3]. A study by Goethaert K et al., showed that the outcome remained the same whether Cefepime or Carbapenems are used for the infections caused by an ESBL-producing *E. aerogenes* in ICU patients [9].

CONCLUSION

Enterobacter spp. is well known to cause nosocomial infections, especially in ICU setting there is increase in incidence. Third generation cephalosporins are mainly implicated in the treatment of *Enterobacter* meningitis whereas fourth generation cephalosporins like Cefepime and Cefpirome can be used to treat resistant *Enterobacter* strains due to faster penetration through outer membrane porin proteins, superior stability to chromosomal β-lactamase and enhanced binding to critical penicillin-binding proteins. Trimethoprim-Sulfamethoxazole and Carbapenems are the limited options available for Cephalosporin resistant *Enterobacter* meningitis.

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