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Spontaneous *Escherichia coli* Meningitis and Pyogenic Ventriculitis in an Adult Receiving Anti-Tumour Necrosis Factor Alpha Therapy

D. Hare[1], D. Doyle[2] A. Doherty[3], M. Creedon[3], E. Houlihan[1], M. Harrison[2], D. Sheppard[4], C. Fleming[5], F. Fitzpatrick[3,6], M. Cormican[1,7]

1. Department of Clinical Microbiology, Galway University Hospital, Galway, Ireland.
2. Department of Respiratory Medicine, Galway University Hospital, Galway, Ireland.
3. Department of Microbiology, Beaumont Hospital, Dublin, Ireland.
4. Department of Radiology, Galway University Hospital, Galway, Ireland.
5. Department of Infectious Diseases, Galway University Hospital, Galway, Ireland.
6. Department of Clinical Microbiology, The Royal College of Surgeons in Ireland, Dublin, Ireland.
7. School of Medicine, National University of Ireland, Galway, Ireland

Abstract

Presentation

A 60-year-old male taking etanercept for ankylosing spondylitis was admitted to hospital with confusion and reduced level of consciousness over the preceding 24 hours.

Diagnosis

Magnetic Resonance Imaging (MRI) of his brain revealed pyogenic ventriculitis, and *Escherichia coli* was cultured from CSF.

Treatment

He required placement of an external ventricular drain and was treated with a prolonged course of intravenous ceftriaxone.

Conclusion

To our knowledge, this is the first reported case of spontaneous Gram-negative bacillary meningitis in a patient on anti-tumour necrosis factor (TNF)-alpha therapy, highlighting the risk of rare but serious infections associated with this class of medication.

Introduction

Gram-negative bacilli are an unusual cause of spontaneous meningitis in adults, which rarely presents as primary pyogenic ventriculitis. Herein we describe a case of spontaneous *E. coli* meningitis presenting with pyogenic ventriculitis, in a patient on anti-TNF-alpha therapy.

Case Report

A 60-year-old male was admitted to hospital with a 24-hour history of confusion and reduced level-of-consciousness, preceded by symptoms of a dry cough and abdominal discomfort for seven days. His medical history was significant only for a diagnosis of ankylosing spondylitis, and he had taken the anti-TNF-alpha inhibitor etanercept for 12 years. Of note, he had not experienced trauma or surgery in the recent past.

On presentation, he was afebrile, Glasgow Coma Scale (GCS) was 13/15 (verbal response 3/5) and physical examination revealed severe neck stiffness. White blood cell count was 22 $x10^9$/L (4-11 $x10^9$/L) (neutrophils $20.9x10^9$/L) and C-reactive protein 404mg/L (0-5mg/L). The presumptive diagnosis was community-onset meningitis and he was commenced on intravenous (IV) ceftriaxone 2 grams 12-hourly, amoxicillin 2g 4-hourly, and vancomycin. Cerebrospinal fluid (CSF) revealed low glucose levels at 0.1mmol/L with significantly elevated protein at 10.34g/L, and microscopy showed numerous Gram-negative bacilli. Magnetic Resonance Imaging (MRI) of his brain revealed ventriculitis, with air-fluid levels in both lateral ventricles consistent with pus (figure 1). On day one, *Escherichia coli* susceptible to amoxicillin was cultured from CSF, and the isolate was subsequently genotyped as ST-144 by genome sequencing using the Illumina MiSeq platform. Cultures of blood and urine remained sterile. On day two, he was transferred to a neurosurgical unit for placement of an external ventricular drain (EVD) and his antibiotic regimen was rationalised to IV ceftriaxone, along with five days of intraventricular gentamicin, 5mg once daily. Serial CSF cultures had sterilised by day seven and the EVD was removed. Computerised Tomography (CT) of his abdomen was also performed; consistent with recent pyelonephritis. By day 27, repeat MRI showed an improvement in his ventriculitis, but an abscess in his left internal capsule (figure 2), not amenable to further drainage.

Figure 1. Axial FLAIR sequence MRI Brain, day 1: Fluid levels within both lateral ventricles likely representative of pus.

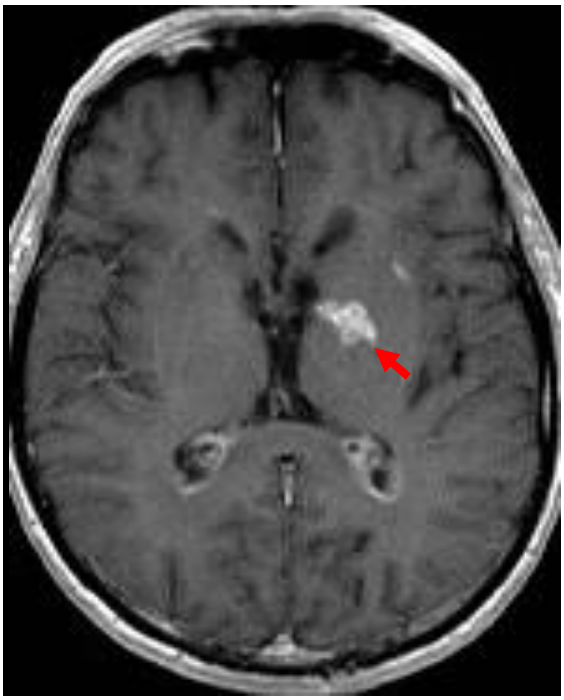

Figure 2. Axial MRI Brain –T1 post-gadolinium, day 27: Evidence of a localised cerebral abscess in the left internal capsule.

Currently, he remains an inpatient and has completed over 12 weeks of IV ceftriaxone. Serial imaging has noted a reduction in the size of the intracerebral abscess, and his GCS has recovered to 15/15 with multi-disciplinary rehabilitation.

Discussion

Gram-negative bacilli (other than *Haemophilus influenzae)* are a rare cause of community-acquired meningitis in adults, responsible for 0.7-7% of cases, and primary pyogenic ventriculitis has rarely been described in the literature[1-3]. According to the Health Protection Surveillance Centre (HPSC), *E. coli* was the pathogen identified in 7% of notified cases of bacterial meningitis in Ireland in 2018, with all cases involving infants aged between 1 and 5 months[4].

Gram-negative bacillary meningitis (GNBM) can be classified as traumatic or spontaneous in origin, with traumatic cases typically occurring in the aftermath of neurosurgery or head injury[5]. Spontaneous GNBM is usually described in patients with identified risk factors such as diabetes mellitus, alcoholism or liver cirrhosis[2,5], and most often arises as a consequence of haematogenous spread from foci such as the urinary tract[6]. Bacteraemia is believed to be a primary determinant for bacterial penetration into the CSF[7] and therefore it is interesting to note the absence of bacteraemia or bacteriuria in this case. Abdominal imaging, however, was suggestive of a urinary source and the *E. coli* was genotyped as ST-144 – a well-described uropathogenic strain[8].

Compared with other meningitides, patients with spontaneous GNBM tend to experience a fulminant clinical course with frequent neurological sequelae, and case fatality rates of 40-60%[2]. Diagnosis can be delayed because clinical features are often non-specific, although bacilli are visible by microscopy in up to 85%, underlining the importance of prompt CSF evaluation[2,6].

Our patient did not have established risk factors for spontaneous GNBM but was immunosuppressed based on taking etanercept – a recombinant receptor fusion protein that binds to TNF-alpha to reduce its bioavailability[9]. TNF-alpha is an important inflammatory cytokine responsible for numerous cellular signalling events, and blockade has been associated with serious bacterial infections, including meningitis caused by *Streptococcus pneumoniae*[9] and *Listeria monocytogenes*[10]. However, to our knowledge, this is the first reported association with spontaneous GNBM.

In conclusion, we describe the first case of spontaneous GNBM with ventriculitis in an adult without risk factors other than anti-TNF-alpha therapy. This serves as a reminder of the risk of rare but serious infections associated with these agents.

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Patient Consent:
Written consent for publication was obtained from the patient prior to submission.

Declaration of Conflicts of Interest:
The authors have no conflicts of interest to declare

Corresponding Author:
Dr Daniel Hare
Specialist Registrar in Clinical Microbiology
Department of Clinical Microbiology,
Galway University Hospital.
E-mail: danielhare5000@gmail.com

References:

1. van de Beek D, de Gans J, Spanjaard L, Weisfelt M, Reitsma JB, Vermeulen M. Clinical features and prognostic factors in adults with bacterial meningitis. N Engl J Med. 2004;351(18):1849-59.
2. Pomar V, Benito N, López-Contreras J, Coll P, Gurguí M, Domingo P. Spontaneous gram-negative bacillary meningitis in adult patients: characteristics and outcome. BMC Infect Dis. 2013;13:451.
3. Gronthoud F, Hassan I, Newton P. Primary pyogenic ventriculitis caused by Neisseria meningitidis: case report and review of the literature . JMM Case Rep. 2017;4(1):e005078.
4. HSE Health Protection Surveillance Centre. Bacterial meningitis, not otherwise specified, in Ireland, 2018. Dublin: HSE HPSC; 2019.
5. Bichon A, Aubry C, Dubourg G, Drouet H, Lagier JC, Raoult D, et al. Escherichia coli spontaneous community-acquired meningitis in adults: A case report and literature review. Int J Infect Dis. 2018;67:70-4.
6. Bouadma L, Schortgen F, Thomas R, Wutke S, Lellouche F, Régnier B, et al. Adults with spontaneous aerobic Gram-negative bacillary meningitis admitted to the intensive care unit. Clin Microbiol Infect. 2006;12(3):287-90.
7. Kim K. Human Meningitis-Associated Escherichia coli. EcoSal Plus. 2016;7(1).
8. Mickiewicz KM, Kawai Y, Drage L, Gomes MC, Davison F, Pickard R, et al. Possible role of L-form switching in recurrent urinary tract infection. Nat Commun. 2019;10(1):4379.
9. Kasirye Y, Epperla N, Manne JR, Bapani S, Garcia-Montilla RJ. Brain abscesses complicating acute pneumococcal meningitis during etanercept therapy. Clin Med Res. 2012;10(4):230-5.
10. Pagliano P, Attanasio V, Fusco U, Mohamed DA, Rossi M, Faella FS. Does etanercept monotherapy enhance the risk of Listeria monocytogenes meningitis? Ann Rheum Dis. 2004;63(4):462-3.