EJCRIM
European Journal
of Case Reports
in Internal Medicine

FROM PRESENTATION TO PROGNOSIS: A CHALLENGING CASE OF MULTIFOCAL CEREBRAL MICRO ABSCESSES DUE TO *CITROBACTER FREUNDII*

Varsha Nandwana, Liam M. Cleary, Thomas V. Kodankandath

Department of Internal Medicine, Section of Neurology, Carilion Clinic-Virginia Tech Carilion School of Medicine, Roanoke, USA

Corresponding author's e-mail: vnandwana@carilionclinic.org

Received: 09/04/2025
Accepted: 14/04/2025
Published: 29/05/2025

Conflicts of Interests: The Authors declare that there are no competing interests.
Patient Consent: We obtained written informed consent from the patient's medical power of attorney to secure permission for publishing their clinical history.
Acknowledgments: We sincerely thank Dr Michael S. Stump for his valuable assistance in the preparation and analysis of histology slides for this report.
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How to cite this article: Nandwana V, Cleary LM, Kodankandath TV. From presentation to prognosis: a challenging case of multifocal cerebral microabscesses due to Citrobacter freundii. *EJCRIM* 2025;**12**:doi:10.12890/2025_005290

ABSTRACT

Introduction: Citrobacter freundii is a rare cause of central nervous system (CNS) infections, primarily affecting neonates. In adults, cases are uncommon and often associated with high mortality rates.

Case description: We describe the case of an adult male with multiple comorbidities who presented with constipation, nausea and vomiting, which rapidly progressed to altered mental status and seizures. Neuroimaging revealed gas densities within intracranial veins and evolving encephalitic changes. Cerebrospinal fluid (CSF) findings were non-specific, but blood and wound cultures identified *C. freundii*. Targeted antibiotic therapy with cefepime and ampicillin-sulbactam was initiated, but the patient's condition deteriorated leading to withdrawal of care, and death. Autopsy confirmed multiple cerebral micro abscesses, consistent with septic embolization.

Conclusion: This case highlights *C. freundii* as a rare but fatal cause of septic encephalopathy. Diagnostic challenges arose from the atypical neurological presentation and non-specific CSF findings. The transition to cefepime was guided by concerns over *C. freundii*'s AmpC β-lactamase production. Despite appropriate antimicrobial therapy, the patient's poor outcome underscored the challenges of managing CNS infections in relatively immunocompromised hosts. Early recognition of *C. freundii* CNS infections is crucial, particularly in high-risk patients. A high index of suspicion, serial imaging and tailored antimicrobial therapy are essential for optimising outcomes. Further research is needed to enhance diagnostic methods and treatment strategies.

KEYWORDS

Citrobacter freundii, brain abscess, central nervous system infections

LEARNING POINTS

- Septic embolization due to *C. freundii* can present with atypical neurological symptoms.
- Antibiotic selection should consider *C. freundii*'s resistance mechanisms.

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INTRODUCTION/BACKGROUND

Citrobacter freundii, a Gram-negative bacterium, is a rare cause of central nervous system (CNS) infections, predominantly affecting neonates and infants. However, cases in adults – though rare – have been documented. In adults, risk factors include multiple facial fractures, neurosurgical procedures, alcoholism and diabetes mellitus[1].

The pathogenicity of *C. freundii* in CNS infections is attributed to its ability to invade and replicate within human brain microvascular endothelial cells. This invasion is dependent on microfilaments, microtubules, endosome acidification and *de novo* protein synthesis. *C. freundii* CNS infections present with diverse neurological symptoms, including encephalopathy, seizures and focal deficits. In adults, the mortality rate of *C. freundii* CNS infections can exceed 50%, often due to delayed diagnosis, intrinsic resistance mechanisms, and the challenges of managing severe sepsis and multi-organ failure in vulnerable populations[2].

We report a rare case of *C. freundii*-associated encephalitis in an adult, highlighting the diagnostic and therapeutic challenges of this uncommon CNS infection.

CASE DESCRIPTION

A 53-year-old man presented to the emergency department with constipation for one week, along with nausea and vomiting for one day. He had a history of end-stage renal disease (on haemodialysis), obstructive sleep apnoea, congestive heart failure, recent COVID-19 infection, type 2 diabetes on insulin and peripheral artery disease with right-sided below-the-knee amputation. Upon arrival, his vital signs were temperature 37°C, heart rate 108 bpm, SpO_2 95% on room air, blood pressure 95/67 mmHg and blood glucose 250 mg/dl. During the initial workup, he developed an altered mental status and was unable to follow commands, prompting a Neurology consultation.

His neurological examination in the emergency department revealed rightward eye deviation, rhythmic eyelid twitching and horizontal right-beating nystagmus. He was given multiple doses of IV midazolam (a total of 12 mg) and loaded with 4,500 mg IV levetiracetam for presumed non-convulsive status epilepticus, after which he was intubated and admitted to the intensive care unit (ICU).

An urgent non-contrast computed tomography (CT) of the head revealed extensive gas densities within intracranial veins *(Fig. 1A)*. A CT angiogram of the head and neck was unremarkable. MRI brain with and without contrast showed a subtly increased signal within the deep white matter of the right frontal lobe, without enhancement and minimal restricted diffusion *(Fig. 1B)*, suggestive of mild localised encephalitis.

A lumbar puncture was performed to rule out CNS infection. Cerebrospinal fluid (CSF) analysis showed a white blood cell count of 3/mm^3 in tube 1 and 0/mm^3 in tube 2, with no red blood cells. Protein was 49 mg/dl, glucose was 108 mg/dl (serum glucose was 158 mg/dl). CSF Gram stain, culture, cryptococcal antigen, HSV-1 and HSV-2 PCR were negative. Blood cultures and a wound culture from a sacral decubitus ulcer revealed 4+ *Citrobacter freundii*, 1+ *Enterococcus faecalis* and 4+ *Prevotella bivia*.

Empirical broad-spectrum antibiotics (vancomycin and piperacillin/tazobactam) were initiated for suspected sepsis. Based on culture results and concern for AmpC β-lactamase production by *C. freundii*, antibiotics were transitioned to cefepime. Metronidazole was added for anaerobic coverage. On day 4, vancomycin and metronidazole were discontinued, and ampicillin-sulbactam was added for Enterococcus coverage. The patient was maintained on renally adjusted levetiracetam (500 mg IV BID) for seizure prophylaxis and required vasopressor support for persistent hypotension; he remained intubated due to altered mental status.

On day 5, a repeat brain magnetic resonance imaging (MRI) showed extensive patchy cortical diffusion restriction in the right frontal and parietal lobes with associated cerebral oedema *(Fig. 2)*, suggesting worsening encephalitis, ischaemic changes or seizure activity. Empirical acyclovir was initiated for possible viral encephalitis.

Despite aggressive management, his condition continued to deteriorate. On day 6, the palliative care team was consulted

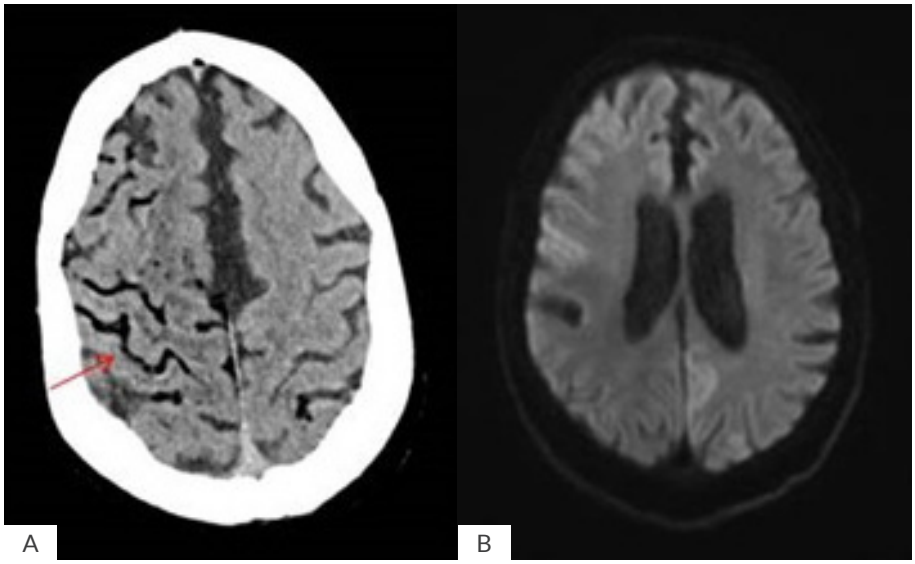


Figure 1. A) NCCT head: gas density within the intracranial veins; B) MRI brain with or without DWI sequence axial section: subtly increased signal within the deep white matter of the right frontal lobe without enhancement with minimal restricted diffusion.

Abbreviations: NCCT, non-contrast computed tomography; DWI, diffusion weighted imaging.

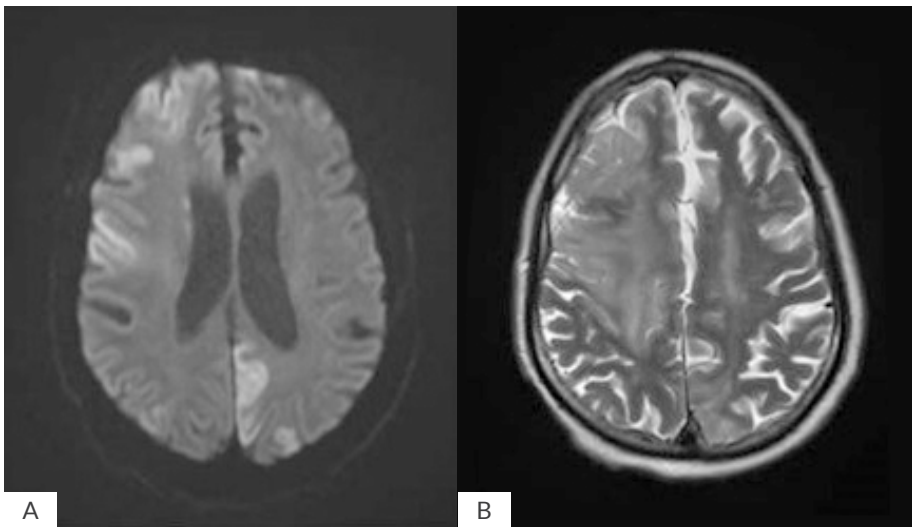


Figure 2. A) MRI brain with or without DWI sequence axial section: extensive patchy increased cortical diffusion signal throughout the right frontal and parietal lobes, and to a lesser degree in the right temporal and occipital lobes and in the posterior left parietal lobe. B) MRI brain with or without T2 sequence axial section: there is associated extensive cerebral oedema in the cortex and the subcortical white matter at the above-mentioned levels.

due to persistent encephalopathy and poor neurological status. After discussions with the medical power of attorney, the patient was transitioned to comfort care and made 'Do Not Resuscitate'. On day 8, the patient was extubated and passed away shortly thereafter.

The autopsy revealed multiple micro abscesses along the grey-white junction of the cerebrum *(Fig. 3)*, predominantly on the right side. Histopathological examination showed histiocytes containing bacteria and separate bacterial colonies, confirming septic embolization. The cause of death was determined to be complications of sepsis due to *C. freundii*.

DISCUSSION

Citrobacter freundii is a facultative anaerobic, Gram-negative bacillus that inhabits soil, water and the gastrointestinal tract. Though commonly associated with nosocomial infections such as urinary tract infections, pneumonia, wound infections and bacteraemia, intracranial involvement secondary to *C. freundii* bacteraemia is exceedingly rare[1].

Few case reports describe its involvement in brain abscess formation, highlighting the significance of this case. Liu et al.[3] described a case of a 73-year-old male with diabetes mellitus who presented with a three-week history of headache and malaise. Imaging revealed an abscess in the left frontal lobe caused by *Citrobacter koseri*, a species closely related to *C. freundii*. After surgical drainage and targeted antibiotic therapy with IV ceftriaxone for six weeks, the patient achieved a complete recovery[3].

Another case report described a 27-year-old woman who presented with fever, status seizures and refractory hypotension. She was diagnosed with *C. freundii* meningitis which progressed rapidly, leading to systemic failure and septic shock. This case illustrates the aggressive nature of *C.*

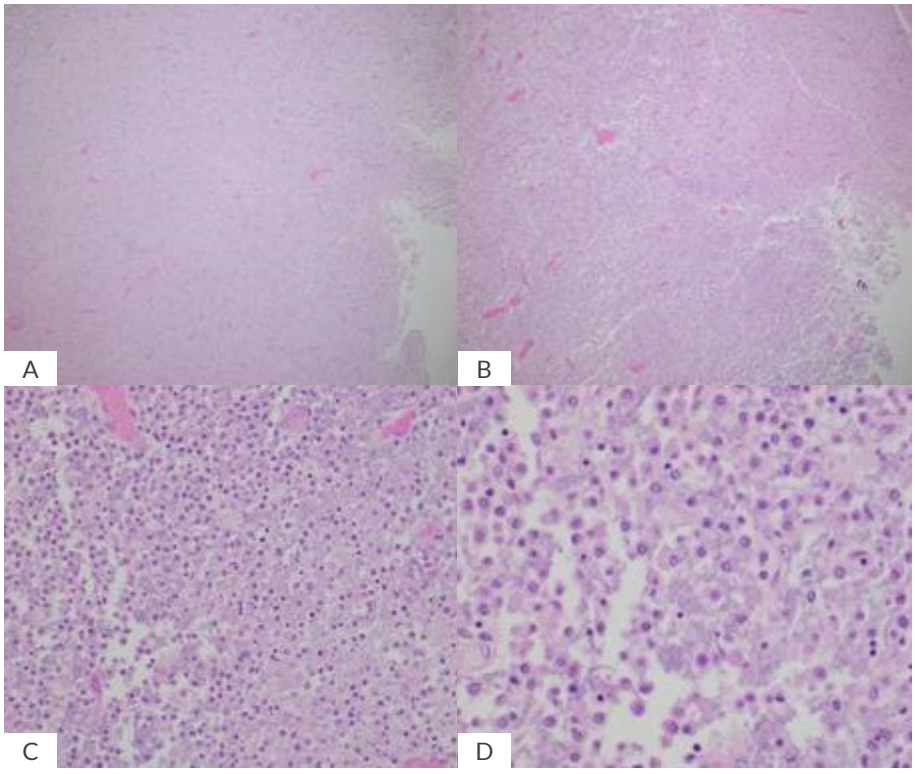


Figure 3. Histology slides, haematoxylin and eosin: A) Representative section of a normal brain, 5×. B) Area of subacute infarct/ necrosis with many histiocytes, 5×. C, D) Many histiocytes containing bacteria: 20× and 40×, respectively.

freundii infections and their association with high mortality rates[4].

The patient's initial gastrointestinal symptoms (constipation, nausea and vomiting) delayed recognition of CNS involvement. This atypical presentation diverted early diagnostic focus away from a neurological aetiology, emphasising the need for vigilance in septic patients with evolving neurological symptoms. The initial CSF findings were non-specific, a common challenge in deep-seated or embolic infections, further complicating early diagnosis. Serial neuroimaging played a crucial role in detecting evolving encephalitic changes, reinforcing the importance of repeated assessments in cases with diagnostic uncertainty. Cefepime was selected for its activity against AmpC β-lactamase-producing *C. freundii*. However, in cases of treatment failure or high-level resistance, alternatives such as meropenem may be required, particularly in critically ill patients with persistent bacteraemia or neurological deterioration[5].

This highlights the necessity of tailoring antimicrobial therapy based on emerging resistance patterns and local susceptibility data. Despite aggressive antimicrobial therapy, the patient's condition worsened, suggesting that micro abscesses may progress despite treatment, particularly in immunocompromised patients with comorbidities such as diabetes, recent COVID-19 infection, end-stage renal disease and sacral decubitus ulcers. This case also illustrates the challenges of managing severe sepsis and multi-organ failure in vulnerable populations, where the margin for error is narrow, and the risk of poor outcomes is high.

CONCLUSION

This case reinforces the recognition of C. freundii as a rare yet severe cause of septic emboli and CNS infection. It highlights the importance of considering intracranial infection in septic patients with altered mental status, the challenges in early diagnosis and the necessity of aggressive yet tailored antimicrobial therapy. The case also underscores the limitations of current diagnostic tools, and the need for a multidisciplinary approach to optimise outcomes. Future research should focus on improving diagnostic methods, such as metagenomic next-generation sequencing (mNGS) of CSF, and exploring adjunctive therapies to enhance the management of severe CNS infections caused by multidrug-resistant pathogens such as C. freundii.

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