The Talking Dead:

Cefepime-Induced Cotard Syndrome

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Cefepime neurotoxicity is a well-documented but underrecognized cause of encephalopathy. The drug's toxic effects result from its ability to cross the blood-brain barrier and antagonize γ-aminobutyric acid A receptors. This report describes a case of cefepime-induced Cotard syndrome, a rare delusional syndrome marked by a persistent belief that one is dead.

Case Report

A 48-year-old woman with a 1-year history of recurrent urinary tract infections (UTIs), nephrolithiasis status post ureteral stenting, and previous encephalopathic episode of unclear etiology presented in January 2023 after a ground level fall at home without loss of consciousness or head trauma. At the time of presentation, she was alert and oriented to self, place, time, and situation. She was found to have a saddle pulmonary embolism and was started on therapeutic anticoagulation in the intensive care unit. Once stable, she was transferred to the general medicine service for management of her pulmonary embolism as well as for a UTI for which she was nearing completion of treatment on a course of cefuroxime. On arrival, she was saturating well without the need for supplementary oxygen. She appeared to be at her mental status baseline. However, she soon developed intermittent fever and asymptomatic hypotension, which prompted a change in therapy to vancomycin and cefepime 2 g twice daily. Infectious workup was unrevealing aside from the UTI. Vancomycin was discontinued after 1 day, but cefepime was continued.

Three days after cefepime was initiated, the patient developed new-onset aphasia and altered awareness. Imaging was negative for acute stroke. Cefepime was discontinued at this time. The following day, the patient was noted to have improved language function and orientation. However, she now endorsed specific delusions, stating she had suffered a heart attack the previous night and was now dead. During cardiac auscultation, the patient stated, "I'm sure you can't hear my heart since I'm dead." When told she would have more blood drawn for testing, she asked, "How can you get my blood if I am dead? There shouldn't be anything in there."

Evaluation of her encephalopathy and subsequent delusions included routine laboratory work and measurement of thyroid-stimulating hormone (TSH), thiamine, and blood gases, which were within normal limits. Kidney function was within normal limits, with serum urea nitrogen at 13 mg/dL and serum creatinine at 1.1 mg/dL. Blood cultures showed no growth, and she tested negative for COVID-19. Computed tomography (CT) scan of the brain, CT scan of the abdomen and pelvis, retroperitoneal ultrasonography, chest x-ray, and echocardiogram were unrevealing. Electroencephalogram (EEG) showed generalized slowing and disorganized background consistent with encephalopathy but no epileptiform abnormalities. She was continued on her current dose of levetiracetam, given inability to rule out non-convulsive seizures. She was discharged with complete resolution of delusions and in stable condition.

Of note, 1 year prior to presentation, the patient was hospitalized for a similar presentation of acute language difficulties and encephalopathy. Before this, the patient had been working as a claims agent for a health insurance company and had no history of mental health problems or substance abuse. She underwent an extensive workup. Brain magnetic resonance imaging with contrast was unrevealing. EEG demonstrated diffuse slowing and abnormal amplitude over the left temporal lobe, but no epileptiform abnormalities. Cerebrospinal fluid laboratory testing showed elevated protein (117 mg/dL), glucose within the normal range (50 mg/dL), and mildly elevated cell count (3/mm^3) with lymphocytic predominance. These findings could be consistent with viral meningitis; however, testing for viral antigens was negative. The remainder of her workup was negative for infectious, autoimmune, metabolic, and vascular etiologies. The psychiatry service was consulted for conversion disorder; however, this was deemed unlikely given no psychiatric history and the abnormal EEG findings. She was ultimately diagnosed with epilepsy and discharged on treatment with an antiepileptic agent; however, there was no actual evidence to support this diagnosis. Following that hospitalization, the patient's chart reveals multiple readmissions for falls and various urologic infections, suggesting a new inability to care for herself, leading to her present illness.

Discussion

This report brings attention to a rare case of Cotard syndrome preceded by general encephalopathy

and aphasia. Given the acute onset of the encephalopathic state following the initiation of cefepime, and the rapid resolution of symptoms with the drug's discontinuation, cefepime neurotoxicity is the most likely inciting factor. An infectious etiology is unlikely given that no infectious source was identified. In fact, it is possible that the patient had not actually been septic, as her instances of fever resolved rapidly, blood cultures were negative, and it was later discovered that the patient had a history of asymptomatic hypotension. Given the patient's history of a previous encephalopathic episode with localized EEG abnormalities, it is possible that the previous episode caused structural or functional derangements to the patient's brain, making her more vulnerable to the effects of neurotoxic substances. She also has a history of insults to her urinary system and multiple hospitalizations for acute kidney injury. Thus, although she was not diagnosed with chronic kidney disease at the time of presentation, it is likely that her kidneys were not filtering her blood optimally.

Cotard syndrome is a delusional misidentification syndrome marked by a persistent belief that one is dead or that one's internal organs are missing.[1] One theory proposes a 2-step mechanism: an initial right hemisphere deficit leads to abnormal internal perception; the left hemisphere then misinterprets this abnormal perception, ultimately resulting in persistent delusions of death or internal disfigurement.[2] Cotard syndrome can present in a wide variety of neurologic disorders, including ischemic stroke, temporal lobe epilepsy,[3] brain tumor,[4] *N*-methyl-D-aspartate encephalitis,[5] subdural hemorrhage,[6] Parkinson disease,[7] and COVID-19,[8] but also following substance withdrawal[9,10] and medication-induced toxicities including those associated with amantadine[3] and valacyclovir.[11] A single case of suspected cefepime-induced Cotard syndrome has been reported in the literature.[12] The evidence for toxic, metabolic, or structural causes of Cotard syndrome is admittedly scarce and is found mostly in case studies. However, rarity itself should not count against the veracity of the accounts. The broad range of offending agents and pathologies points instead to the fact that, in Cotard syndrome, the identity of the dysfunctional brain circuits is more important than the inciting factor resulting in the dysfunction.

In addition to delusions of death, Cotard syndrome is commonly associated with depression and suicidality, features that were notably absent in our case. While depression is a common feature, a subset of patients with this condition present with primarily psychotic features in the absence of depression.[13] The use of antipsychotics and electroconvulsive therapy has demonstrated efficacy in treating Cotard delusions. No treatment was necessary in our patient given the spontaneous resolution of her symptoms after discontinuing cefepime, the presumed inciting medication. Cotard syndrome is a potentially treatable disorder often attributed to hospital-acquired delirium due to its rarity and unusual presentation. However, if recognized, it could reveal an underlying neurologic disorder or drug toxicity. Prompt recognition by the physician is important for improved outcomes.

Article Information

Published Online: December 7, 2023. https://doi.org/10.4088/PCC.23cr03573

Prim Care Companion CNS Disord 2023;25(6):23cr03573

Submitted: May 27, 2023; accepted August 14, 2023.

To Cite: Orr S, Lazris D, Very B, et al. The talking dead: cefepime-induced Cotard syndrome. *Prim Care Companion CNS Disord*. 2023;25(6):23cr03573.

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Relevant Financial Relationships: None.

Funding/Support: None.

Acknowledgments: The authors thank the patient, family, and neurology team.

Patient Consent: Consent to publish this case report was received from the patient and a family member. Information has been de-identified to maintain anonymity.

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