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Case Report

Ceftriaxone-Induced Encephalopathy in an Elderly Patient with Low Serum Creatinine: A Case Report

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Abstract

Antibiotic-associated encephalopathy induced by ceftriaxone (CTRX), a third-generation cephalosporin, is a serious adverse event primarily reported in patients with severe renal dysfunction or in those receiving hemodialysis. We encountered an elderly patient in her 80s who developed impaired consciousness while receiving CTRX 2 g/day for bacteremia secondary to a deep neck abscess despite having a low serum creatinine (SCr) level of 0.53 mg/dL at the initiation of CTRX therapy. Altered mental status emerged on day 11 of CTRX therapy. Brain imaging, cerebrospinal fluid analysis, and electroencephalography revealed no alternative etiology, raising concerns of CTRX-induced encephalopathy, and the drug was discontinued on day 23. Cystatin C, measured on day 18, was markedly elevated at 3.62 mg/dL, suggesting significant renal dysfunction, which was not captured by the SCr-based assessment. Furthermore, the plasma CTRX concentration at discontinuation was profoundly elevated at 158.3 μg/mL, indicating substantial accumulation of CTRX and supporting its role as the primary cause of encephalopathy. The patient's mental status improved, along with a reduction in plasma CTRX concentration. This case highlights the fact that in older adults with low SCr values, reliance on SCr alone may lead to an overestimation of renal function, particularly in patients experiencing acute muscle wasting following intensive care. Therefore, incorporating cystatin C-based renal assessment prior to or early in treatment may facilitate proactive dose adjustment, potentially preventing the onset of CTRX-induced encephalopathy.

Key words: ceftriaxone, antibiotic-associated encephalopathy, serum creatinine, cystatin C, elderly patient

Introduction

Ceftriaxone (CTRX) is a third-generation cephalosporin broad spectrum antibiotic that is widely used in clinical practice. However, several reports have described cases of antibiotic-associated encephalopathy caused by CTRX, characterized by neurological manifestations such as impaired consciousness, seizures, myoclonus, and coma, particularly in patients with severe renal impairment or those undergoing hemodialysis[1].

Serum creatinine (SCr) levels are commonly used to assess renal function. However, as SCr levels are affected by muscle mass, elderly individuals with reduced muscle mass often exhibit low SCr levels. Consequently, the estimated creatinine clearance (eCCr) calculated using the Cockcroft-Gault equation and the estimated glomerular filtration rate based on serum creatinine (eGFRcr) may overestimate renal function[2].

In contrast, cystatin C, a low-molecular-weight protein produced at a constant rate by all nucleated cells, is freely filtered through the glomeruli, reabsorbed by proximal tubular cells, and subsequently catabolized. As it is not excreted in the urine, its serum concentration reflects glomerular filtration. Compared with SCr, cystatin C levels are less affected by diet, muscle mass,

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sex, or age and are therefore considered a more reliable biomarker of renal function in elderly patients with sarcopenia[3].

This case report describes CTRX-induced encephalopathy in an elderly patient with low SCr levels, in whom renal function was overestimated by SCr-based indices but accurately reflected by cystatin C measurements. The patient developed impaired consciousness during CTRX therapy. Both elevated plasma CTRX concentrations and improvement after CTRX discontinuation supported the diagnosis of CTRX-induced encephalopathy.

Ethical considerations

This case report was conducted with full consideration of personal data protection in accordance with the Guidance for Appropriate Handling of Personal Information by Medical and Nursing Care Providers (Ministry of Health, Labour and Welfare) and the Guidelines for Protecting Patient Privacy in Medical Papers and Conference Presentations, Including Case Reports (Council of Surgical Societies in Japan). Written informed consent was obtained from the patient's family. This report was approved by the Ethics Committee of Toyooka Public Hospital (Approval No. 456).

Case Presentation

An elderly patient in her 80s, 155 cm in height, and weighing 67 kg (BMI 27.9), who was independently undertook activities of daily living, presented with bacteremia caused by *Streptococcus constellatus* and a deep neck abscess. The patient's past medical history included hypertension, dyslipidemia, and lumbar spinal canal stenosis. The patient had been taking candesartan cilexetil (4 mg), pravastatin sodium (5 mg), and amlodipine besylate (5 mg), once daily after breakfast. The patient did not drink alcohol, had no history of smoking, and had no known drug allergies or prior adverse drug reactions.

The patient noticed swelling and pain on the right side of her neck three days before admission, followed by dyspnea the next day. On the morning of admission (day 1), the patient's symptoms worsened, prompting emergency transportation to the hospital.

Upon arrival, the patient's Glasgow Coma Scale (GCS) score was E4V4M6. Contrast-enhanced computed tomography revealed an abscess extending from the right mandibular region to the perijugular space, with increased mediastinal fat density, suggestive of an early infectious focus.

Under tracheal intubation, incision and drainage were performed, and blood and pus samples were collected for culture. Empirical antibiotic therapy was initiated with meropenem, vancomycin, and clindamycin. Because of septic shock, norepinephrine was administered and continuous hemodiafiltration (CHDF) was initiated for renal support in the intensive care unit (ICU). Sedation was maintained with midazolam and analgesia with fentanyl, resulting in a GCS of E1VTM1. Despite escalating norepinephrine doses, the patient's hemodynamic status deteriorated, suggesting septic cardiomyopathy; therefore, veno-arterial extracorporeal membrane oxygenation (VA-ECMO) and intra-aortic balloon pumping (IABP) were initiated. Thyroid function tests (TSH 0.95 mIU/L, free T4 1.09 mIU/L) were within normal limits.

Her urine output on day 2 was 1.2 mL/kg/h under CHDF. On day 4, *S. constellatus* was isolated from both blood and pus cultures, and *Prevotella intermedia* and *Dialister pneumosintes* were identified from the pus. Based on the susceptibility results, antibiotic therapy was switched to ampicillin/sulbactam (ABPC/SBT) on day 7. VA-ECMO was discontinued on day 6, midazolam was tapered with the addition of dexmedetomidine, and the IABP was removed on day 8. However, inflammatory markers increased again, prompting readministration of meropenem on day 9 and placement of a left thoracic drain. The inflammatory response subsequently improved, and a tracheostomy was performed on day 12. Midazolam was discontinued; however, fentanyl infusion was continued for wound pain management. CHDF was discontinued on day 13 when the urine output was 0.9 mL/kg/h.

By day 16, the patient's consciousness had improved to GCS E3VTM6, and sepsis was controlled. The antibiotic therapy was switched to CTRX 2 g/day on day 19. Dexmedetomidine was discontinued on day 24, irrigation and drainage of the cervical abscess continued, and CTRX was maintained. The urine output remained at 0.7–0.8 mL/kg/h.

On day 29 (11th day of CTRX), the patient developed persistent eye closure and decreased responsiveness to verbal commands, with the GCS score declining to E1VTM2. Notably, typical symptoms of antibiotic-associated encephalopathy, such as seizures or myoclonus, were not observed. Brain magnetic resonance imaging (MRI) revealed no structural abnormalities.

Cerebrospinal fluid analysis on day 31 (13th day of CTRX) showed clear, colorless fluid without pleocytosis (protein 88 mg/dL, glucose 71 mg/dL, cell count 7/μL). On day 34 (16th day of CTRX), fentanyl was discontinued because drug accumulation was considered a possible cause of the altered mental state; however, intravenous administration of 0.4 mg naloxone did not result in any improvement in the patient's GCS score. Electroencephalography (EEG) on the same day revealed diffuse slow waves without epileptiform discharges. The causality of the adverse drug reaction was evaluated using the Naranjo algorithm[4]. The score for CTRX-induced encephalopathy was calculated as 7 points (Probable). Conversely, the score for fentanyl was 1 point (Possible), as the administration of naloxone did not improve the patient's consciousness.

Based on these findings, CTRX accumulation secondary to renal dysfunction was suspected to be the cause of CTRX-induced encephalopathy. The cystatin C level measured on day 36 (18th day of CTRX) was available on day 41, and showed a marked increase to 3.62 mg/dL. The eGFR cystatin C (eGFRcys) calculated using the equation provided by the Japanese Society of Nephrology[3] corresponded to 10.3 mL/min/1.73 m^2. Based on this finding, CTRX was discontinued on day 41, and the antibiotic therapy was switched back to ABPC/SBT.

After the discontinuation of CTRX, the patient's consciousness gradually improved: GCS E2VTM4 on day 49 (9 days post-discontinuation) and GCS E4VTM6 on day 57 (17 days post-discontinuation). Cystatin C levels decreased to 2.19 mg/dL on day 55 and 1.8 mg/dL on day 62. Plasma CTRX concentrations measured by high-performance liquid chromatography-mass spectrometry were 158.3 μg/mL on day 41 (day of discontinuation), 10.5 μg/mL on day 49 (9 days post-discontinuation), and 0.6 μg/mL on day 57 (17 days post-discontinuation). The clinical findings are summarized in Fig. 1.

Discussion

This case report describes an elderly patient with

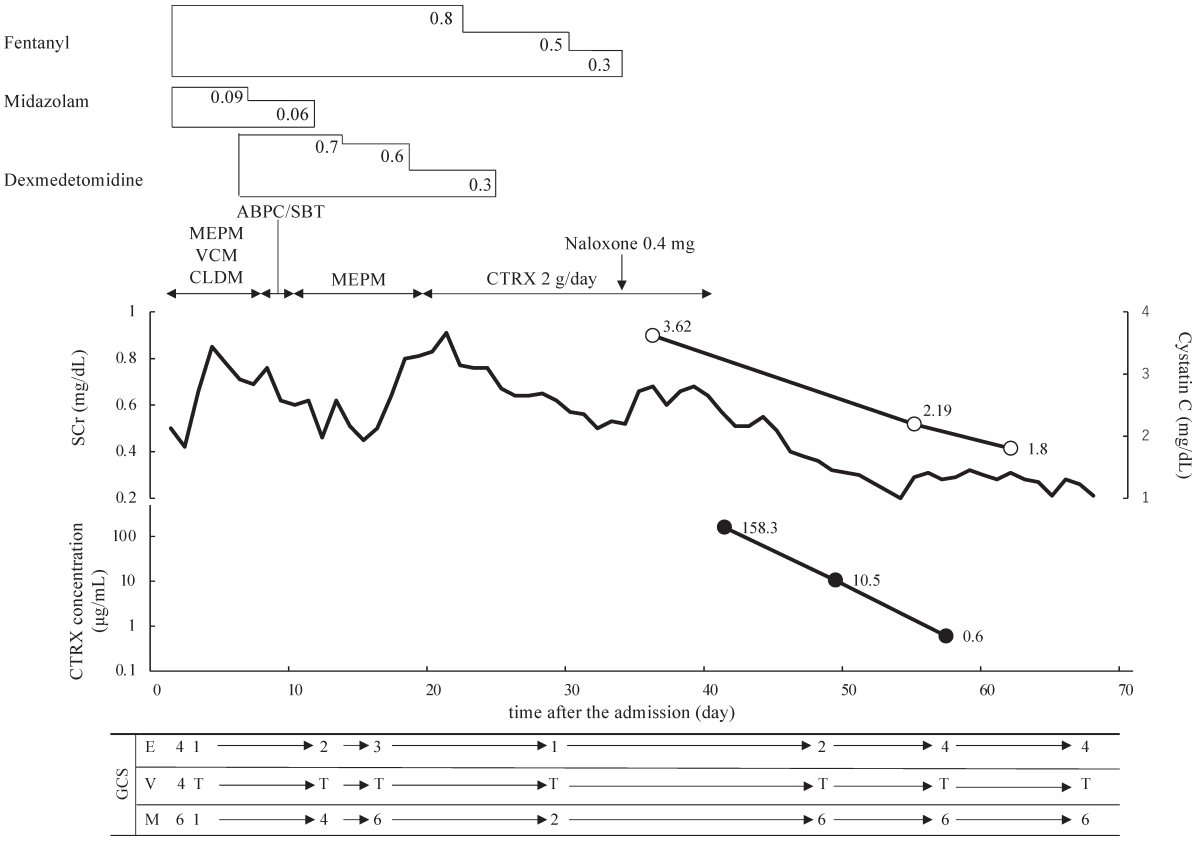


Fig. 1　Time-course of the plasma ceftriaxone concentrations (●), SCr levels (solid line), cystatin C levels (○) and Glasgow Coma Scale scores.
Fentanyl unit: μg/kg/h
Midazolam unit: mg/kg/h
Dexmedetomidine unit: μg/kg/h

low SCr levels who developed impaired consciousness on day 11 of continuous CTRX administration (2 g/day), which improved after CTRX discontinuation. Although SCr-based indices did not indicate renal impairment, markedly elevated cystatin C and decreased eGFRcys levels revealed significant renal dysfunction. The concurrent high plasma CTRX concentration strongly suggested that CTRX-induced encephalopathy was the principal cause of the neurological symptoms.

A national pharmacovigilance database analysis in Japan reported that CTRX-induced encephalopathy occurs more frequently in females and is associated with higher doses (≥ 2 g/day) and prolonged administration[5]. The patient met these criteria and was, therefore, considered to be at high risk. Previous cases of CTRX-induced encephalopathy typically involved patients with overt renal impairment as defined by SCr-based eCCr or those on hemodialysis[6~8]. In contrast, this patient's low SCr (0.53 mg/dL measured on day 19, at the initiation of CTRX therapy) yielded apparently normal eCCr and eGFRcr values, leading to overestimation of renal function. A study in ICU patients demonstrated that the accuracy of eCCr calculated using the Cockcroft-Gault equation was only approximately 47% compared with the measured 24-hour urinary creatinine clearance[9].

Thus, reliance on SCr alone may be inadequate for evaluating renal function in the elderly or critically ill patients, and cystatin C measurement should be considered for a more accurate assessment.

Because SCr is influenced by muscle mass, it tends to be low in elderly individuals. However, in this case, the discrepancy between SCr and cystatin C was likely driven not only by chronic sarcopenic obesity[10] but also by acute muscle wasting secondary to profound stress. The patient required CHDF for septic shock from day 1 to 13. This highly invasive prolonged ICU stay likely caused rapid muscle atrophy, completely exhausting SCr production and thereby masking ongoing acute kidney injury (AKI). The reversibility of cystatin C (decreasing from 3.62 mg/dL to 1.8 mg/dL after day 41) strongly suggests that the renal impairment was a dynamic recovery process from shock- or vancomycin-induced AKI, rather than merely static chronic kidney disease. Furthermore, we selected CTRX 2 g/day on day 19 to ensure adequate tissue penetration for the deep neck abscess, mistakenly relying on the seemingly normal SCr. Retrospectively, given the patient's vulnerable renal status shortly after CHDF weaning, earlier evaluation using cystatin C would have prompted an initial dose reduction, potentially preventing the development of encephalopathy. Furthermore, while the improvement of cystatin C after CTRX discontinuation implies recovery from shock- or vancomycin-induced AKI, the possibility that CTRX itself contributed to the exacerbation of AKI cannot be entirely ruled out.

The normal reference range for cystatin C is 0.5–1.0 mg/dL[11]. The elevated cystatin C level (3.62 mg/dL) corresponded to an eGFRcys of 10.3 mL/min/1.73 m^2, clearly indicating renal impairment. Although corticosteroids, cyclosporine, and hypothyroidism can increase cystatin C[2], none of these factors were present, suggesting that the elevated value reflected true renal dysfunction.

The therapeutic plasma concentration range for CTRX is 0.7–8.0 μg/mL[12], while concentrations of 60–700 μg/mL have been associated with CTRX-induced encephalopathy onset[13]. In this case, on day 34, fentanyl was discontinued and naloxone was administered, with no improvement in the GCS score. According to the Naranjo scale[4], the causality for fentanyl was low (1 point) because of the lack of response to the specific antagonist. Therefore, an altered mental state due to fentanyl administration was objectively ruled out. On the other hand, the Naranjo score for CTRX was high (7 points), strongly supported by the onset of symptoms following CTRX administration, the markedly elevated plasma CTRX level of 158.3 μg/mL, and the parallel improvement of mental status with decreasing plasma CTRX concentrations after discontinuation. Therefore, an altered mental state due to fentanyl administration was ruled out. On the other hand, the CTRX level of 158.3 μg/mL measured one day after discontinuation was markedly elevated, consistent with reported CTRX-induced encephalopathy cases. The patient's mental status improved in parallel with the decreasing plasma CTRX concentrations, supporting this association. Based on pharmacokinetic analysis of three data points (158.3 μg/mL, 10.5 μg/mL, 0.6 μg/mL), the elimination half-life was calculated at 48.4 hours — considerably longer than the reported 5.8–8.7 hours in patients with normal renal function[14] — indicating that renal impairment contributed to accumulation of CTRX.

Previous reports on CTRX-induced encephalopathy[15]

have demonstrated elevated cerebrospinal fluid CTRX concentrations as confirmatory evidence. In this case, high plasma CTRX concentrations were recorded, and clinical symptoms, including absence of MRI abnormalities, diffuse EEG slow waves, onset of impaired consciousness within two weeks of treatment, and improvement after discontinuation were observed. Thus, the patient was suspected to have Type I antibiotic-associated encephalopathy, the subtype commonly associated with cephalosporins[16]. Furthermore, regarding the relationship between decreased renal function and impaired consciousness, the possibility of uremic encephalopathy secondary to acute kidney injury must be considered.

While sepsis, mechanical circulatory support, fentanyl exposure, and uremic encephalopathy due to declining renal function may have contributed to the patient's altered mental status, the combination of markedly elevated plasma CTRX concentrations, confirmed renal dysfunction based on cystatin C, and clear improvement after CTRX withdrawal strongly supports CTRX-induced encephalopathy as the primary etiology.

This case highlights the fact that in older adults with low SCr values, reliance on SCr alone may lead to an overestimation of renal function, particularly in patients experiencing acute muscle wasting following intensive care. Therefore, incorporating cystatin C-based renal assessment prior to or early in treatment may facilitate proactive dose adjustment, potentially preventing the onset of CTRX-induced encephalopathy.

Conflict of Interest

There are no conflicts of interest to disclose regarding this report.

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