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Magnetic resonance imaging (MRI) and computed tomography angiography (CTA) assisted diagnosis of cytotoxic lesions of the corpus callosum (CLOCC) mimicking Splenial Infarction: A case report

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► ***Case report***

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ABSTRACT

Cytotoxic lesions of the corpus callosum (CLOCC) represent secondary injuries associated with various clinical etiologies. These lesions, characterized by restricted diffusion on cranial magnetic resonance imaging (MRI), manifest as small and reversible abnormalities in the splenium of the corpus callosum. Despite their distinct radiological features, they often pose a diagnostic challenge, mimicking acute cerebral infarction in clinical presentation. Herein, we present the case of a 47-year-old male with a history of two episodes of transient syncope, transient bilateral blindness, multiple episodes of diarrhea, and high fever. Initially suspected to have acute splenial infarction secondary to sepsis and gastrointestinal infection, further evaluation including cranio-cervical computed tomography angiography (CTA) and electroencephalography, in conjunction with neurology consultation, led to the diagnosis of CLOCC. Prompt initiation of antimicrobial and antipyretic therapy resulted in rapid neurological improvement within 48 hours. Splenial lesions in the context of sepsis often masquerade as infarction due to their association with coagulopathy and microvascular thrombosis. However, emerging evidence suggests that isolated infarction in this region is exceedingly rare, with reversible lesions characteristic of CLOCC being more commonly encountered. Management primarily entails addressing the underlying systemic condition, with a generally favorable prognosis observed in most cases.

INTRODUCTION

In the wake of the COVID-19 pandemic, there has been a notable increase in the identification of rare neurological abnormalities [1] associated with CLOCCs. These lesions, also referred to as Mild Encephalopathy with Reversible Splenial Lesion (MERS), Reversible Splenial Lesion Syndrome (RESLES), among other names, constitute a distinct clinical entity characterized by transient abnormalities within the corpus callosum [2], typically detected through restricted diffusion on MRI, with a predilection for the splenium region [3]. The literature increasingly documents CLOCCs as neurological manifestations linked to various clinical contexts.

CLOCC is a condition characterized by reversible lesions in the corpus callosum observed on MRI [4]. CLOCCs show high-signal-intensity on T2-weighted (T2) images, fluid-attenuated inversion recovery images (FLAIR), and diffusion-weighted images (DWI) with restricted diffusion and without contrast enhancement on T1-weighted imaging. They tend to be midline and are relatively symmetric [5, 6]. These MRI abnormalities typically resolve within days to weeks, although clinical recovery may sometimes require a longer duration. There are various terms used to describe cytotoxic lesions of the corpus callosum, including Mild Encephalitis/ Encephalopathy with Reversible Splenial Lesion (MERS), Reversible Splenial Lesion Syndrome (RESLES), reversible corpus callosum lesion, transient corpus callosum lesion, asymptomatic corpus callosum lesion, and transient focal lesion of the corpus callosum [7]. Compared to other parts of the brain, the corpus callosum, especially the splenium, has a higher density of receptors, including cytokine receptors, toxin receptors, and drug receptors in neurons, astrocytes, and oligodendrocytes, making it more susceptible to cytotoxic edema [8, 9]. Therefore, various factors such as infections, seizures, sudden discontinuation of antiepileptic drugs, metabolic abnormalities, stroke, certain drug therapies, head trauma, malignancies, multiple sclerosis, subarachnoid hemorrhage, and

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hypoglycemia can lead to CLOCC [10].

CLOCCs are associated with diverse factors such as infections, abrupt cessation of antiepileptic drugs, metabolic disorders, cerebral infarctions, exposure to certain drugs, traumatic brain injury, malignancies, multiple sclerosis, subarachnoid hemorrhage, and hypoglycemia [10]. These factors may initiate a pathophysiological cascade resulting in cytotoxic edema due to increased intracellular sodium and calcium levels [2]. However, clinical cases directly attributing sepsis to the development of CLOCCs remain lacking.

Sepsis poses a significant challenge in critical care medicine, often leading to multiple organ dysfunction syndrome (MODS) and high mortality rates despite advancements in medical management [11]. Among the complications associated with sepsis, central nervous system (CNS) involvement is increasingly recognized as a significant contributor to morbidity and mortality [12]. While the mechanisms of CNS injury in sepsis are multifaceted, ranging from direct infection to metabolic disturbances and microvascular thrombosis [13], the manifestation of CLOCCs represents a distinct yet underreported entity in this context.

This paper presents a case study of a patient who developed sepsis secondary to gastrointestinal infection, resulting in CLOCCs. The patient exhibited transient neurological symptoms, including syncope and bilateral blindness, initially misdiagnosed as isolated splenial infarction. However, further diagnostic evaluation, including CTA and electroencephalography, elucidated the underlying pathology, underscoring the importance of comprehensive assessment in distinguishing CLOCCs from other neurological conditions.

Grasping the breadth of clinical conditions associated with CLOCCs, particularly in the milieu of systemic infections, is imperative for precise diagnosis and timely intervention. This case underscores the necessity for heightened awareness among clinicians concerning the diverse presentations of CLOCCs and the pivotal role of interdisciplinary collaboration in optimizing patient care and outcomes.

The present study presents a unique case that underscores the challenges and opportunities in diagnosing and treating CLOCCs. Our detailed account of the patient's clinical course, the complexities of the diagnostic journey, and the timely therapeutic intervention provide novel insights into understanding and managing such rare lesions. Furthermore, this research emphasizes the critical role of interdisciplinary collaboration in optimizing patient care, especially in managing complex and uncommon clinical presentations. Additionally, our findings illuminate the pathophysiological mechanisms of CLOCCs within the spectrum of sepsis, including the release of inflammatory cytokines and local osmotic changes. The favorable outcome following prompt recognition and treatment suggests that rapid identification and intervention can significantly improve patient prognosis, potentially influencing future treatment guidelines.

CASE PRESENTATION

A 47-year-old male patient was admitted to the emergency department. He had no history of trauma or surgery prior to hospitalization. He has a two-year history of hypertension, with a maximum blood pressure record of 160/100 mmHg. He is currently taking oral antihypertensive medications, including sustained-release metoprolol succinate and amlodipine/valsartan combination tablet, which effectively control his blood pressure below 140/90 mmHg.

He had a history of long time swimming in a reservoir before the onset of symptoms. He complained of recurrent fever over the past three days. On the second and third day, he experienced two episodes of transient syncope, followed by transient visual loss upon awakening. On the day of admission, he also complained of several episodes of watery diarrhea, but without abdominal pain or bloating. Body temperature was 37.2°C, blood pressure of 100/70mmHg, and oxygen saturation of 97% at the time of admission. He was conscious and cooperative, with equal eye pupils and bilaterally reactive to light. His tongue was in the midline, and no power loss was observed. The Babinski test was negative in the physical examination and no tremor or dyskinesia was noticed.

Significant increases were observed in the percentage of neutrophils (90.2%, normal range: 40%-75%), erythrocyte sedimentation rate (37 mm/h, normal range: 0-15mm/h), C-reactive protein (205.6mg/L, normal range: 0.0-8.0 mg/L), and procalcitonin (10.580 ng/ml, normal range: <0.500 ng/ml) in the complete blood count. Obvious decreases were observed in the absolute value of total T lymphocytes (173 cells/μl, normal range: 797-2370 cells/μl), the absolute values of helper/inducer T cells (84 cells/μl, normal range: 432-1341 cells/μl), and suppressor/cytotoxic T cells (85 cells/μl, normal range: 238-1075 cells/μl). Significant elevation were observed in the level of Interleukin-6 (28.41 pg/ml, normal range: 0.00-2.90 pg/ml), Mild elevations in creatinine (140 umol/L, normal range: 44-97 umol/L), and moderate reductions in glomerular filtration rate (51.18 ml/min, normal range: >90.00 ml/min). Obvious hyperglycemia (11.45 mmol/L, normal range: 3.90-6.10 mmol/L) was present, as well as elevated fibrinogen levels (5.81 g/L, normal range: 2.38-4.98 g/L). No abnormalities were found in other laboratory tests, including glycated hemoglobin, antinuclear antibodies (ANA) , double-stranded DNA (ds-DNA) , urine analysis, stool exam and culture, liver function tests, electrolytes, Human

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Immunodeficiency Virus (HIV) 1 and 2 screen, hepatitis series, D-dimer, blood gas analysis, cardiac enzyme profile, and troponin T (TnT-hs). Chest and head Computed Tomography (CT, GE BrightSpeed, USA) scans excluded pneumonia and intracranial hemorrhage.

Given the patient's medical history encompassing episodes of transient syncope, temporary loss of vision, and fever, it is imperative to consider potential diagnoses such as acute intracranial lesions, severe infection, cardiogenic syncope, and epilepsy. To ascertain the underlying cause of syncope, a several diagnostic approach was undertaken, involving brain CT scan and magnetic resonance imaging (MRI, MAGNETOM Skyra 3T, Siemens, Erlangen, Germany), electroencephalogram (EEG, BrainCap MR, Brain Products, Gilching, Germany), echo-Doppler examination of the carotid arteries, electrocardiogram (ECG, HOLTER 7.0 GOLD, USA), 24 -hour Holter monitoring (NEC - 3321, JPN), and Doppler echocardiogram. Given the presence of fever and diarrhea upon admission, chest CT and contrast-enhanced abdominal CT scans were conducted in order to ascertain the origin of the infection. No instances of lung infection, intracerebral haemorrhage, intracranial infection, brain tumour, malignant arrhythmias, or epilepsy were detected; however, isolated splenial lesions in the corpus callosumwere observed. Axial T1-weighted imaging (T1WI) revealed an isolated, elliptical low-signal-intensity lesion located in the splenium of the corpus callosum (figure 1A), suggesting the presence of cytotoxic edema or other pathological processes. Transverse T2-weighted imaging (T2WI) of the same lesion showed increased signal intensity (figure 1B), typically associated with higher water content, indicative of edema or inflammation. These signal changes support the diagnosis of CLOCCs, which frequently exhibit high signal intensity on T2WI. Diffusion-weighted imaging (DWI) demonstrated significant high signal in the splenium (figure 1C), a sensitive indicator of acute lesions such as cytotoxic edema or acute infarction. The apparent diffusion coefficient (ADC) map displayed reduced diffusion in the splenium (figure 1D), consistent with the high signal on DWI, further suggesting the presence of intracellular edema. Three-dimensional reconstruction and axial CTA images showed no evident abnormalities in the patient's cerebral vasculature (figures 1E and 1F), excluding vascular lesions as the cause of the splenial lesion. This exclusion further supports the diagnosis of CLOCCs, as CLOCCs typically do not involve vascular structural changes. The patient's abdominal CT scan showed the presence of large infiltrative lesions surrounding both kidneys, bilateral thickening of the renal fascia, and diffuse enlarged lymph nodes in the hepatic hilum, greater omentum, and retroperitoneum (figure 2).

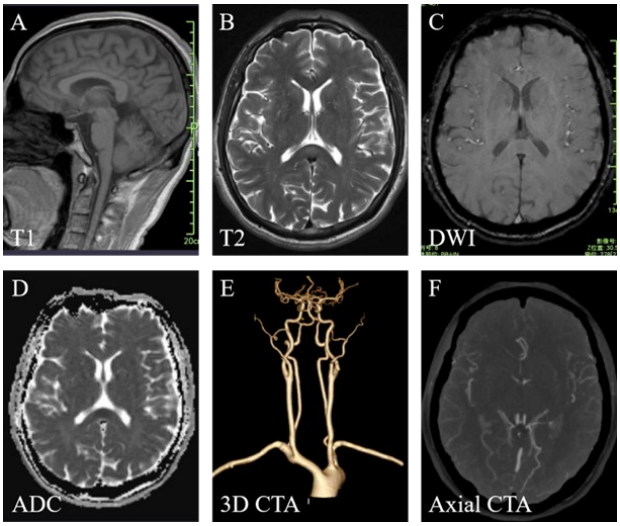

Figure 1. Brain MRI and CTA. **(A)** Axial longitudinal relaxation time-weighted imaging (T1WI) show isolated splenial ovoid lesion of low signal intensity; **(B)** transverse relaxation time-weighted imaging (T2WI) show higher signal intensity at the same location; **(C)** diffusion-weighted imaging (DWI) show splenial hyperintensity, and **(D)** apparent diffusion coefficient (ADC) show reduced diffusion restriction at splenium of the corpus callosum; **(E)** Three-dimensional reconstruction and **(F)** Axial CTA shows no obvious abnormalities.

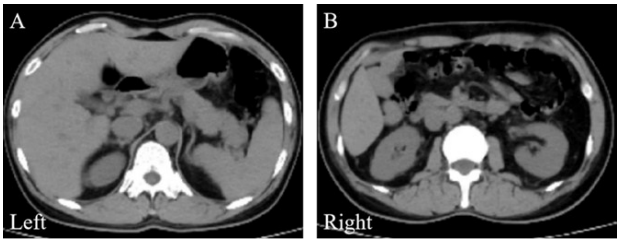

Figure 2. Abdominal CT scan. **(A)** Left figure shows the presence of diffuse enlarged lymph nodes in the hepatic hilum, greater omentum, and retroperitoneum; **(B)** right figure shows the presence of large infiltrative lesions surrounding both kidneys, bilateral thickening of therenal fascia.

The findings from the gastrointestinal symptoms and auxiliary examinations indicate that a gastrointestinal infection preceded an intra-abdominal infection, ultimately leading to sepsis and the development of isolated splenial ischemic damage. Empirical doses of piperacillin sodium-tazobactam sodium were initiated, and blood cultures were obtained prior to antibiotic therapy initiation. Given the rarity of isolated splenial infarction, consultation with a neurologist was advised. As a precautionary measure, aspirin antiplatelet therapy was empirically initiated, followed by CTA. The CTA results showed no abnormalities in the patient's cerebrovascular system (Figure 1E and F). A second opinion from a different neurologist, based on the CTA result, suggested that the patient's condition may mimic splenial infarction but could be a CLOCC caused by direct toxic damage to the brain from sepsis. The recommended treatment primarily involves systemic antibiotics, with or without steroidal anti-inflammatory therapy.

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On the second day after receiving anti-infection therapy, the patient's temperature normalized, and neurological symptoms such as syncope and visual abnormalities improved.

Two weeks after cessation of antibiotic therapy, blood culture results returned negative for bacterial growth. At the 2-week post-discharge follow-up, the patient reported no recurrence of fever, diarrhea, syncope, or visual abnormalities, indicative of a successful recovery. With regards to the potential reversibility of CLOCCs, it was recommended to undergo a follow-up cranial MRI. However, the patient declined further evaluation, leading to the loss of some pertinent medical records.

DISCUSSION

In this case report, we present a 47-year-old male patient who developed CLOCC, a condition often linked with various clinical scenarios and misinterpreted as acute cerebral infarction due to its appearance on cranial magnetic resonance imaging (MRI). The patient exhibited symptoms including transient syncope, transient bilateral blindness, diarrhea, and high fever, leading to an initial diagnosis of sepsis, gastrointestinal infection, and suspected acute splenial infarction. Further CTA examination and consultation with a neurology specialist confirmed the presence of CLOCCs in the splenium.

The case discussed in this paper involves a patient with sepsis, where inflammation originating from an abdominal infection led to sepsis, subsequently affecting the splenium of the corpus callosum. To date, there have been no reports of sepsis causing isolated corpus callosum injury; hence, it is often misdiagnosed as acute cerebral infarction during initial diagnosis. However, the rapid response to antimicrobial and antipyretic therapy within 48 hours suggests a reversible state, consistent with findings in the literature regarding CLOCCs [1]. Wilson *et al*. investigated the causes of corpus callosum diffusion restriction and found that non-vascular cases often occurred in younger individuals with fewer vascular risk factors [14]. Our focus on the splenium highlights its susceptibility to cytokinopathy and cytotoxic edema, contributing to diffusion restriction as seen in conditions like CLOCCs [14]. While ischemic infarction is rare in the corpus callosum as a whole [15] but can rarely occur in the splenium [16, 17]. The propensity for diffusion restriction, whether cytotoxic or infarct-mediated, can complicate the determination of the underlying cause. Previous research has found that lateralized splenial and multifocal areas of diffusion restriction are more indicative of a vascular etiology, aiding in the differentiation between cytotoxic and ischemic causes [14].

Sepsis poses a significant challenge in critical care medicine, often leading to multiple organ dysfunction syndrome (MODS) and high mortality rates despite advancements in medical management [18]. Among the complications associated with sepsis, central nervous system (CNS) involvement is increasingly recognized as a significant contributor to morbidity and mortality [19]. While the mechanisms of CNS injury in sepsis are multifaceted, ranging from direct infection to metabolic disturbances and microvascular thrombosis [20], the manifestation of CLOCCs represents a distinct yet underreported entity in this context. Based on the transient and reversible nature of rapid progression from symptoms to recovery in patients following antibiotic therapy, it is hypothesized that CLOCC is related to hemodynamic abnormalities and the release of inflammatory cytokines caused by sepsis. The absence of bacterial growth in blood cultures and resolution of symptoms post-antibiotic treatment may implicate a transient pathology linked to sepsis-induced systemic inflammatory response rather than a direct infectious process. According to literature reports, the mechanism underlying such corpus callosum changes involves stress-induced increases in extracellular cytokines and glutamate, leading to elevated intracellular sodium and calcium levels, thereby promoting intracellular edema [2]. This local edema results in osmotic changes, often fluctuating and reversible, distinct from the persistent tissue death seen in cerebral infarctions.

The link between sepsis, coagulation dysfunction, and microvascular thrombosis with the presentation of splenial lesions misdiagnosed as infarction underscores the necessity for a comprehensive diagnostic approach that includes a thorough clinical history, MRI findings, and consultation with specialists. This multidisciplinary approach facilitates the differentiation between CLOCCs and cerebral infarctions, guiding appropriate therapeutic strategies aimed at treating the underlying condition rather than the symptomatic infarct-like manifestation. Furthermore, the reversible nature of the lesion associated with CLOCCs, as opposed to the often irreversible damage caused by cerebral infarctions, suggests a favorable prognosis when correctly identified and managed, highlighting the potential for full recovery with adequate and prompt treatment.

In conclusion, this case underscores the importance of vigilant assessment and interdisciplinary approaches in diagnosing and managing CLOCCs, particularly in patients with acute neurological symptoms and peculiar MRI findings, highlighting the need for further research to improve diagnostic accuracy and patient outcomes.

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***Authors' contributions*:** C.L.and H.Z. designed the study and performed the experiments; H.Z. and H.X. collected the data; H.X. and Q.C. analyzed the data; C.L.and H.Z. prepared the manuscript. All authors read and approved the final manuscript.

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