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Case Report

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Cytotoxic Lesions of the Corpus Callosum (CLOCC): Four Case Reports

Korpus Kallozumun Sitotoksik Lezyonları: Dört Vaka Sunumu

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ABSTRACT

The corpus callosum serves as the primary commissural region of the brain, comprising white matter tracts that facilitate interhemispheric communication between the left and right cerebral hemispheres. It consists of approximately 200 million heavily myelinated axons, which form homotopic or heterotopic projections to contralateral neurons within the same anatomical layer. The corpus callosum is conventionally divided into four distinct parts: the rostrum, genu, body, and splenium. These components connect corresponding centers in the right and left cerebral hemispheres, thereby enabling comprehensive neural coordination.

Cytotoxic lesions of the corpus callosum (CLOCC) represent unusual clinical conditions characterized by diverse presentations. This study presents four cases of CLOCC. The first case involved a 41-year-old male patient who presented with symptoms of fever, blurred vision, and fatigue. The second case concerned a 21-year-old female patient who presented with headache, fever, tinnitus, and sore throat. The third case involved a 65-year-old female patient who presented with headache, focal seizures with impaired awareness, and confusion. The fourth case involved a 64-year-old female who presented with global aphasia and right hemiparesis; she developed a fever during clinical follow-up.

Upon evaluating the etiology of CLOCC, an undetermined infection following a dental procedure was identified in the first case, lobar pneumonia in the second case, and sinus venous thrombosis in the third case. Additionally, the third case developed epileptic seizures during follow-up. In the fourth case, a bacterial infection of undetermined origin that resolved with empirical antibiotic therapy was considered the etiology. Diagnosis involves identifying acute diffusion restriction in the corpus callosum using diffusion MRI. CLOCC should be considered in the differential diagnosis of patients presenting with undiagnosed neurological findings. These lesions are often reversible and have a favorable prognosis, depending on the underlying cause. Radiological identification is crucial for selecting appropriate treatment options.

Keywords: Corpus callosum; Cytotoxic lesions; Magnetic resonance imaging.

ÖZET

Korpus kallozum, her iki serebral hemisfer arasında interhemisferik iletişimi sağlayan, beyaz cevher traktlarının oluşturduğu birincil komissüral alandır. Korpus kallozum, yaklaşık 200 milyon ağır miyelinli aksondan oluşur ve kontralateral nöronlara homotopik veya heterotopik projeksiyonlar oluşturur. Anatomik olarak, korpus kallozum dört ayrı bölüme ayrılır: rostrum, genu, body ve splenium. Bu bileşenler, sağ ve sol serebral hemisferlerin karşılık gelen merkezlerini bağlar ve kapsamlı nöral koordinasyonu sağlar.

Korpus kallozumun sitotoksik lezyonları (KKSL), çeşitli nörolojik semptomlarla kendini gösterebilir. Bu çalışmada dört KKSL vakası sunulmaktadır. İlk vaka, nöroloji polikliniğine ateş, bulanık görme ve yorgunluk şikayetleriyle başvuran 41 yaşında erkek hastaydı. İkinci olgu, 21 yaşında kadın hasta, acil servise baş ağrısı, ateş, tinnitus ve boğaz ağrısı ile başvurdu. Üçüncü vaka, 65 yaşındaki bir kadın hastaydı. Acil servise baş ağrısı, farkındalığın bozulduğu

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fokal nöbet ve konfüzyon ile başvurdu. Dördüncü vaka, 64 yaşında kadın hastaydı; global afazi ve sağ hemiparezi ile başvurdu ve acil servisteki takibinde ateş ortaya çıktı.

Korpus kallozum splenium lezyonunun (KKSL) etiyolojisinde, ilk vakada diş temizleme işlemi sonrası gelişen enfeksiyon, ikinci vakada lobar pnömoni ve üçüncü vakada sinüs venöz trombozu tespit edildi. Ayrıca üçüncü vakada takip sırasında ateş ve farkındalığın bozulduğu nöbetler izlendi. Dördüncü vakada ise ampirik antibiyotik tedavisine yanıt veren, ancak kültür ve görüntüleme gibi enfeksiyon odağına yönelik tetkiklerde kaynağı tespit edilemeyen bakteriyel enfeksiyonun etiyolojide rol oynadığı düşünüldü. KKSL tanısı, difüzyon manyetik rezonans görüntüleme (MRI) kullanılarak korpus kallozumda akut difüzyon kısıtlamasının belirlenmesiyle konur. KKSL, tanı konulmamış nörolojik bulguları olan hastalarda ayırıcı tanıda göz önünde bulundurulmalıdır. Genellikle altta yatan nedene bağlı olarak geri dönüşümlüdür ve iyi prognozludur. Radyolojik olarak tanınması, uygun tedavi seçimi için önemlidir.

Anahtar sözcükler: Korpus kallozum; Manyetik rezonans görüntüleme; Sitotoksik lezyon.

The corpus callosum is the primary commissural region of the brain, comprising white matter tracts that facilitate interhemispheric communication between the left and right cerebral hemispheres. It is composed of approximately 200 million heavily myelinated nerve fibers, which form homotopic or heterotopic projections to contralateral neurons within the same anatomical layer.[1] Anatomically, from anterior to posterior, the corpus callosum is divided into four distinct parts based on previous histological findings: the rostrum, genu, body, and splenium. Each of these components is responsible for connecting distinct areas of the cortex, thereby enabling the integration and transfer of sensory, motor, and high-level cognitive signals between the hemispheres.

Cytotoxic lesions of the corpus callosum (CLOCC) represent unusual clinical conditions characterized by diverse presentations. These lesions are secondary to various entities including drug therapy, malignancy, infection, subarachnoid hemorrhage, metabolic disorders, trauma, and other conditions. Although the incidence of CLOCC is not precisely known, reported rates vary between 1.1% and 3% in several studies.[2] However, as magnetic resonance imaging (MRI) is difficult to perform in all patients, this result may be underestimated. CLOCC may manifest non-specific symptoms such as fever, vomiting, diarrhea, headache, urinary retention, and mild mental changes. In some cases, severe manifestations like mental changes and epileptic seizures may occur. Although the etiology of CLOCC is not fully understood, it is hypothesized that cell–cytokine interactions leading to markedly increased levels of cytokines and extracellular glutamate may contribute to the dysfunction of callosal neurons and microglia.[3,4] The etiology of CLOCC is not fully known.[3]

We herein present four cases of CLOCC. The informed consent form was obtained from the participants.

Case Report

Case 1 — A 41-year-old male patient presented to the Neurology clinic with symptoms of blurred vision. Notably, he had undergone dental cleaning three days prior to his presentation, and a day after the procedure, he developed a fever of 38.5°C, blurred vision, and fatigue. His medical history was significant for diabetic retinopathy, type II diabetes mellitus, and coronary artery disease. Upon examination, his visual acuity was found to be 20/25 in the right eye and 20/50 in the left eye. Other neurological and systemic examination findings were unremarkable, except for an elevated body temperature of 38.2°C. Blood and microbiological tests were conducted, revealing a C-reactive protein (CRP) level of 8.77 mg/L and a procalcitonin level below 0.02 ng/mL. Empirical antibiotic therapy was initiated based on these findings. Magnetic resonance imaging (MRI) of the brain revealed a lesion in the midsection of the corpus callosum splenium. On the fluid-attenuated inversion recovery (FLAIR) sequence, a hyperintense nodular focus was observed, which demonstrated diffusion restriction on diffusion-weighted imaging (DWI), indicative of cytotoxic edema (Fig. 1). At the 20-day follow-up, the patient's blurred vision had resolved, and a control brain MRI showed complete normalization of the previously observed lesion.

Case 2 — A 21-year-old female patient presented to the Emergency Department with symptoms of headache, fever, tinnitus, and sore throat. Her body temperature was elevated at 39.0°C, while other vital signs and neurological and systemic examinations were unremarkable. Diffusion magnetic resonance imaging (MRI) revealed acute focal diffusion restriction in the midsection of the splenium, indicative of a cytotoxic lesion of the corpus callosum (Fig. 2). A lumbar puncture was performed, which did not reveal any abnormalities in the cerebrospinal fluid. The patient was diagnosed with lobar pneumonia, confirmed by thoracic com-

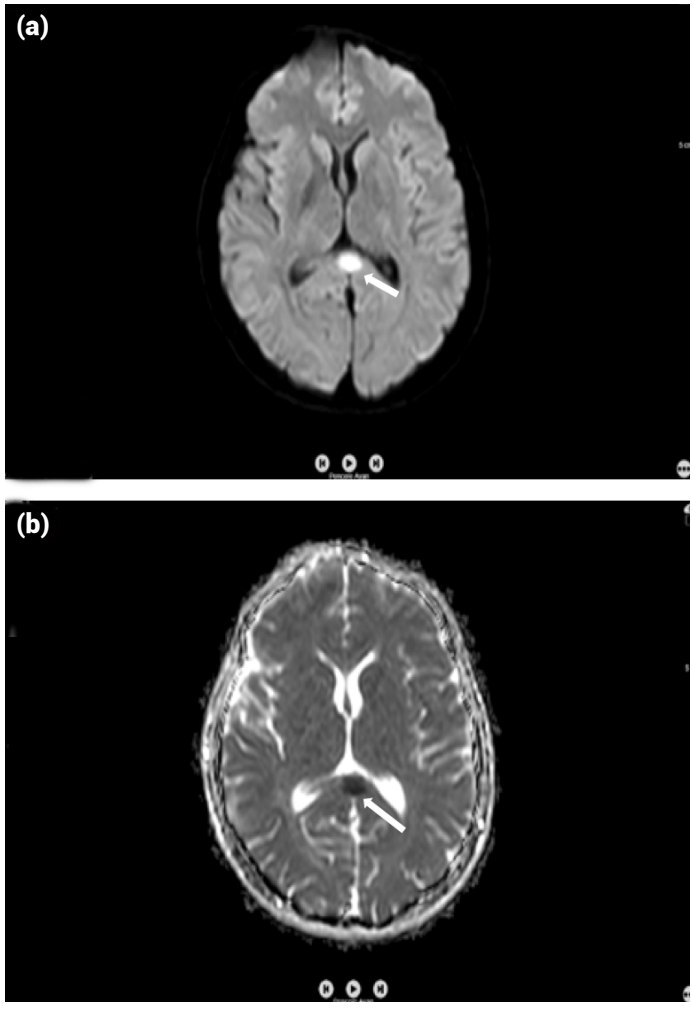

Figure 1. Case 1; **(a)** Arrow showing nodular acute diffusion restriction in the splenium of the corpus callosum on diffusion MRI; **(b)** The corresponding anatomical parts exhibited drop-out hypointense character on the apparent diffusion coefficient (ADC) mapping.

puted tomography (CT). She was initiated on ceftriaxone and moxifloxacin therapy and admitted to the neurology ward. Following antibiotic treatment, her symptoms completely resolved. Brain MRI conducted one week later demonstrated normalization of the previously observed lesion.

Case 3 — A 65-year-old female patient presented to the Emergency Department with symptoms of headache and focal seizures accompanied by confusion. The neurological examination revealed confusion, disorientation, and mild bilateral papilledema, while systemic examination findings were unremarkable. Initial vital signs were within normal limits. Diffusion-weighted magnetic resonance imaging (MRI) demonstrated a focal lesion in the splenium of the corpus callosum, resulting in mild diffusion restriction (Fig. 3). Additionally, MR venography showed decreased flow

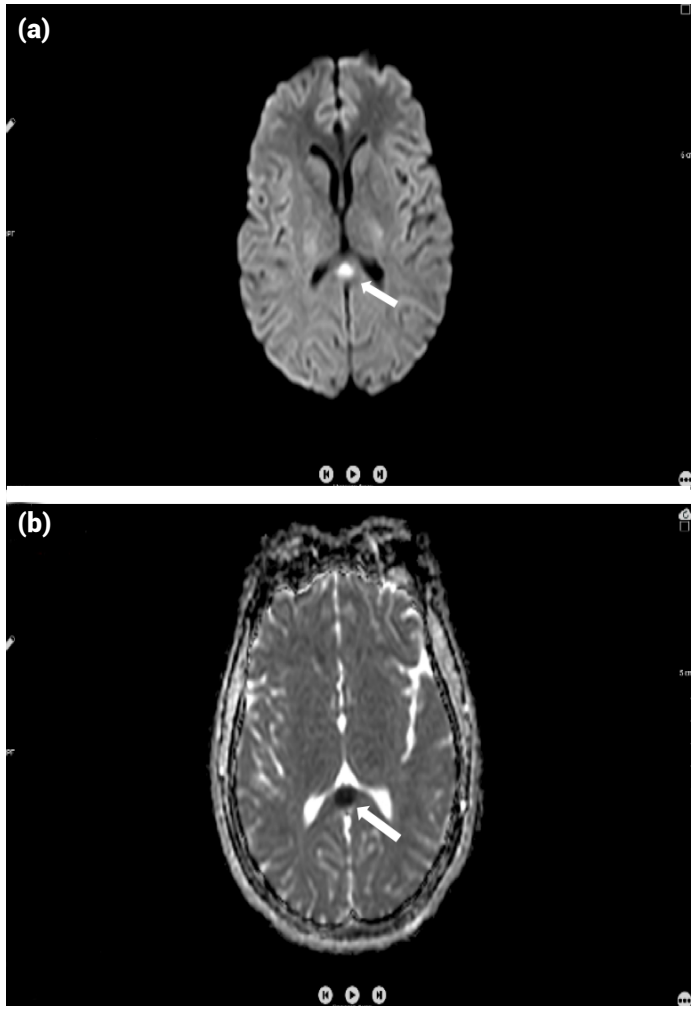

Figure 2. Case 2; **(a)** Acute diffusion restriction in the corpus callosum on diffusion MRI; **(b)** The corresponding anatomical parts exhibited hypo intensity on the ADC.

in the cerebral deep veins and inferior sagittal sinus, suggesting venous thrombosis. The patient was admitted to the neurology ward and initiated on antiepileptic therapy with levetiracetam and anticoagulant therapy with warfarin. During follow-up, her symptoms resolved, she experienced no further seizures, and her neurological examination findings returned to normal. One month later, a follow-up diffusion MRI revealed complete normalization of the previously observed lesion.

Case 4 — A 64-year-old female patient with a medical history of type 2 diabetes mellitus, idiopathic hypertension, and coronary artery disease presented to the Emergency Department with symptoms of global aphasia, right hemiparesis, and fever. Her vital signs were within normal limits except for an elevated body temperature of 38.2°C, and she was normoglycemic. The neurological examination revealed no signs of meningeal irritation. The patient was conscious

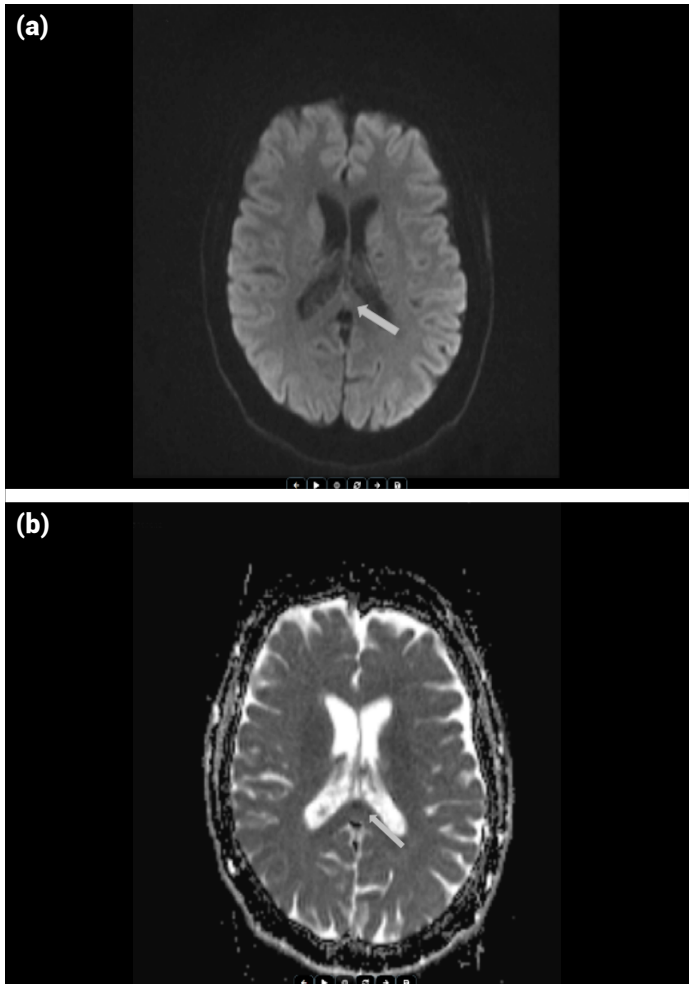

Figure 3. Case 3: **(a)** Acute diffusion restriction in the splenium of the CC on diffusion MRI showed by an arrow; **(b)** The corresponding area is showed hypo intensity on the ADC.

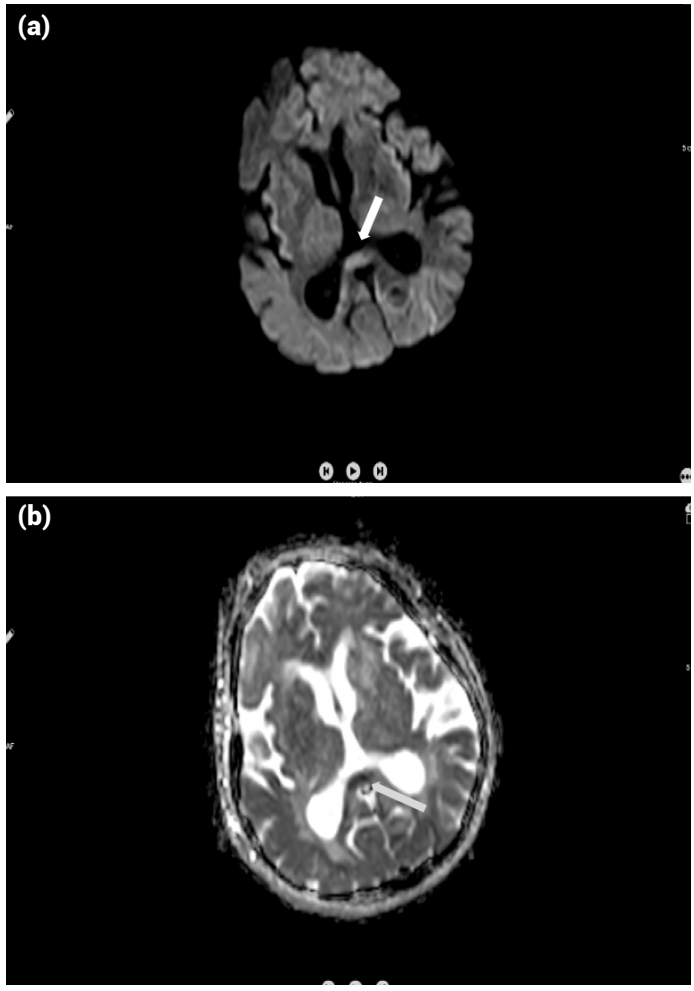

Figure 4. Case 4: **(a)** Acute diffusion restriction in the splenium of the corpus callosum on diffusion MRI; **(b)** Hypointense lesion was showed by an arrow on ADC.r54esw.

but drowsy, globally aphasic, with right hemiparesis and a positive Babinski reflex on the right side. Initial diffusion-weighted magnetic resonance imaging (MRI) was unremarkable. A lumbar puncture was performed, and cerebrospinal fluid infection parameters were found to be negative. Empirical antibiotic therapy was initiated after culture samples were obtained. Due to persistently elevated blood pressure, the patient was admitted to the intensive care unit (ICU).

The following day, the patient experienced focal seizures with impaired awareness and was started on levetiracetam. An electroencephalogram (EEG) showed slowing background activity in the right hemisphere. During follow-up, no further seizures occurred, and blood pressure remained normotensive, although there was no improvement in neurological examination findings. Two days after ICU admission, a brain MRI revealed diffusion restriction in the splenium of the corpus callosum (Fig. 4). The patient was transferred to the neurology ward six days later. On the same day, she developed delirium and was screened for metabolic disorders, but no significant pathologic biochemical abnormalities were found. Blood tests for autoimmune encephalitis were sent. A subsequent diffusion MRI showed that the lesion had been resolved. Two days later, the patient's delirium, aphasia, and right hemiparesis were resolved. The autoimmune encephalitis panel returned negative. Twenty days after discharge, the patient was seen in a neurology outpatient clinic with no complaints, and her neurological examination was normal.

Discussion

CLOCC are usually reversible and associated with various etiologies.[5] A review reported that the most associated condition was epilepsy, followed by infection.[3] Various infections can cause CLOCC.[2,6] After the COVID-19 pan-

demic, the prevalence of infection-related cases has increased.[2,7] In a recently published study, neuroimaging was performed on 167 patients with neurological symptoms out of a total of 3404 COVID-19 patients, and it was reported that the most common lesions were splenial lesions.[7] Other common causes of CLOCC are seizure, head trauma, and metabolic problems like hyponatremia. Despite the unclear exact pathophysiology of CLOCC, it is proposed that reversible cellular fluid mechanism failures, cytotoxic edema, focal demyelination, and inflammatory changes could be involved.[6]

The primary diagnostic tool for CLOCC is brain MRI. Typical MRI features are reversible hyperintense signal change on T2-weighted images, fluid-attenuated inversion recovery images, diffusion-weighted images, decreased apparent diffusion coefficient (ADC) values on ADC map, and hyper–isointense signals on T1-weighted images without contrast enhancement. Most imaging findings disappear within 2 weeks.[8] These types of MRI findings suggest cytotoxic edema, but most of them disappear completely without sequelae.[4] According to the lesion type, size, and location, they are classified into three patterns as follows: (1) a small round or oval lesion in the center of the splenium, (2) a lesion in the splenium extending into the adjacent white matter, or (3) a lesion in the splenium extending into the anterior portion of the CC (the boomerang sign).[4]

As brain MRI may not be performed in all patients, diagnosis may be difficult. Demyelination (e.g. multiple sclerosis), infarction (e.g. pericallosal artery occlusion), intoxication, posterior reversible encephalopathy syndrome (PRES), head trauma (e.g. diffuse axonal injury), acquired immunodeficiency syndrome (AIDS), lymphoma, cerebral fat embolism, vitamin B12 and folate deficiency should be considered in the differential diagnosis.[3]

The prognosis of CLOCC depends on the underlying causes. Generally, the outcomes are quite well.[2,6] Some MRI studies have suggested complete recovery within one month, often within one week of clinical improvement.[8]

For treatment, there have been reports of immunotherapy such as steroids and immunoglobulin, along with supportive care for the underlying disease, or treatment with prophylactic antibiotics and antivirals.[9,10] However, no differences were observed in clinical recovery and prognosis depending on the treatment method.[10]

When our cases are evaluated in general, all patients presented with fever. Upon evaluating the etiology of CLOCC, an undetermined infection following a dental procedure was identified in the first case, lobar pneumonia in the second case, and sinus venous thrombosis in the third case. Additionally, the third case developed epileptic seizures during follow-up. In the fourth case, a bacterial infection of undetermined origin that resolved with empirical antibiotic therapy and high blood pressure were considered as the etiology.

Conclusion

In conclusion, corpus callosum lesions with restricted diffusion (CLOCCs) are rare and can arise from various etiologies, including infections (especially after COVID-19 pandemics, case notifications related to infection and post-vaccination incidents have been reported), metabolic and electrolyte abnormalities, drug usage, epilepsy, and cerebrovascular diseases. Therefore, CC lesions should be considered in patients presenting with undiagnosed neurological signs and symptoms. It is important to note that brain MRI is a valuable advanced imaging technique for diagnosing these lesions. Clinicians should be familiar with the imaging appearance of CLOCCs to avoid a misdiagnosis. When CLOCCs are found, the underlying cause of the lesion should be sought and addressed.

Disclosures

Ethics Committee Approval: This is a single case report, and therefore ethics committee approval was not required in accordance with institutional policies.

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