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Case Report

Cytotoxic Lesions of the Corpus Callosum: A Case Series

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Abstract

Various clinical conditions such as encephalitis, spontaneous intracranial hypotension, childbirth, trauma, use of antipsychotic and chemotherapeutic drugs, and subarachnoid hemorrhage may cause high-signal lesions in the splenium of the corpus callosum on diffusion-weighted imaging, which are referred to as cytotoxic lesions of the corpus callosum. In this article, we aimed to present the cytotoxic lesions of the corpus callosum, which were detected incidentally in patients who underwent brain magnetic resonance imaging for different reasons in our center.

Keywords: Corpus callosum, cytotoxic lesion, MRI, neuroimaging

INTRODUCTION

Cytotoxic lesions of the corpus callosum (CLOCCs) are clinical–radiological conditions characterized by a specific magnetic resonance imaging (MRI) pattern. Causes of CLOCCs include various entities such as drug therapy, malignancy, infection, subarachnoid hemorrhage, metabolic disorders, trauma, spontaneous intracranial hypotension, and the early postpartum period.[1-4] Since CLOCCs are secondary lesions associated with various clinical conditions, it is important for radiologists to know their causes in order to guide treatment.

In general, MRI shows a round lesion in the mid-splenium of the corpus callosum that is hyperintense on T2-weighted (T2W)/fluid-attenuated inversion recovery (FLAIR) sequences. Lesions show no enhancement on contrast-enhanced (CE) T1-weighted images (T1WI). The most important imaging finding is the restricted diffusion in diffusion-weighted imaging (DWI). In CLOCCs, the CC can be affected in 3 different patterns: 1) a round/oval lesion in the center of the splenium; 2) a lesion extending from the mid-splenium to either side with commissural fibers; and 3) a lesion extending from the splenium to the body of the CC.[5] We report here 5 cases of CLOCCs with different causes.

CASE PRESENTATION

Case 1

A 50-year-old man with orthostatic headache presented with severe headache and nausea. On physical examination, he was conscious and oriented, and no deficits in muscle strength and dizziness were observed. The patient underwent cranial MRI (Figures 1A-G) and magnetic resonance venography (MRV) (Figure 1H). MRI revealed a subdural hematoma (SDH) in the right hemisphere, subdural effusion in the left hemisphere, thinning of the lateral ventricles, 5 mm displacement of the cerebellar tonsils caudally at the level of the foramen magnum, and narrowing of the mamillopontine space (3 mm) (Figures 1A-E). There was a well-circumscribed, round-shaped non-enhancing lesion in the splenium of the CC (Figures1A-E), which was hyperintense on T2W/FLAIR sequences and was accompanied by marked restricted diffusion (Figures 1F and G). Post-contrast MRI images revealed leptomeningeal enhancement of the brain (Figures 1D and E). In addition, cortical veins, superior and inferior sagittal sinuses, and sinus rectus were prominent on the cranial MRV (Figure 1H). The findings were consistent with the diagnosis of intracranial hypotension. Lumbar epidural blood patch treatment was performed with 25 mL of autologous venous blood at the L4–L5 intervertebral level, and burr-hole evacuation was performed for SDH. After the procedures, the orthostatic headache improved, and the patient was discharged.

Case 2

A 19-year-old female applied to the emergency department of our institution with confusion after falling off a horse. The values of laboratory tests, including a hemogram, renal and liver function tests, and a serum electrolyte analysis, were within normal limits. The patients brain computed tomography revealed linear hemorrhagic densities in the subcortical white matter of both frontal lobes (Figure 2). An oval-shaped T2W/FLAIR hyperintense lesion (Figure 3A) with restricted diffusion on DWI (Figures 3B and C) was observed in the splenium of the CC. Multiple hemorrhagic foci were detected in bilateral periventricular and subcortical white matter on susceptibility-weighted imaging (SWI) images (Figures 3D-F). Findings were consistent with posttraumatic diffuse axonal injury and CLOCCs. The patient received levetiracetam, cefazolin, haloperidol, and mannitol treatment for 4 days. The patient's consciousness improved after the treatment, and she was discharged on the fifth day.

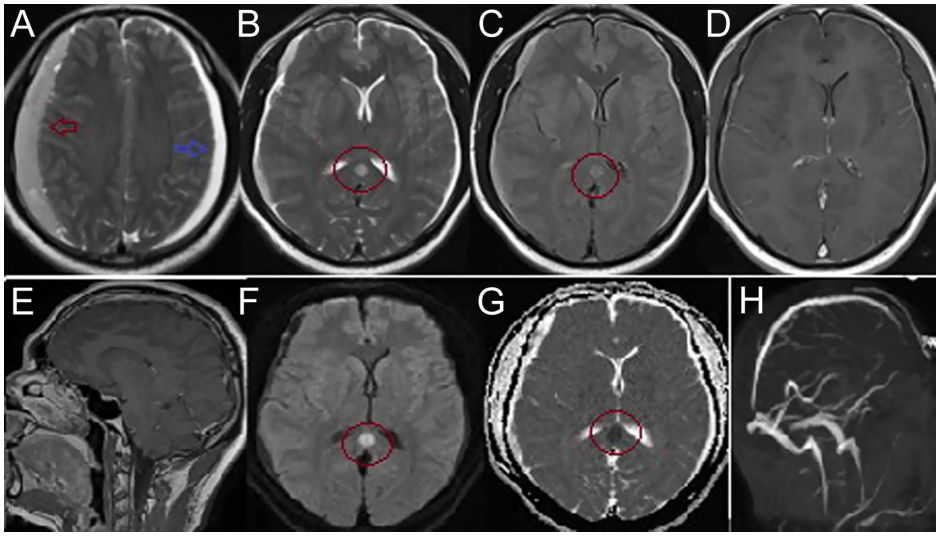

Figure 1. T2-weighted axial image (A) shows a subdural hematoma in the right hemisphere (red arrow) and subdural effusion in the left hemisphere (blue arrow). Axial T2-weighted (B) and fluid-attenuated inversion recovery (C) images demonstrate a round focal hyperintense lesion in the mid-splenium of the corpus callosum (circles). Axial (D) and sagittal (E) contrast-enhanced T1-weighted images show a lack of lesion enhancement but diffuse leptomeningeal enhancement. The lesion reveals restricted diffusion with a hyperintense signal on the diffusion weighted image (F, circle) and hypointensity on the apparent diffusion coefficient map (G, circle). Axial images (B-D) show thinning of the lateral ventricles. There is a caudal displacement in the cerebellar tonsils on the sagittal contrast-enhanced T1-weighted image (E). Enlargement of the cortical veins, superior and inferior sagittal sinuses, and sinus rectus was observed in cranial magnetic resonance venography (H).

Case 3

A 30-year-old female presented with headache and bilateral temporary visual impairment episodes lasting for 1 week on the 20th day of the postpartum period. She had no history of neurological disease or hypertension. No abnormality was observed in neurological and ophthalmological examinations. Complete blood count parameters and blood biochemical tests, including thyroid hormone and cholesterol levels, were normal. Although mean ambulatory blood pressure measurements were normal, spot-high values were detected in the range of 160-170/100-110 mm Hg. Mild proteinuria was detected in the patient's urinalysis. Based on clinical and laboratory findings, it was diagnosed as late-onset preeclampsia. There was an ovoid T2W/FLAIR hyperintense splenial lesion (Figures 4A and B) showing restricted diffusion with markedly low apparent diffusion coefficient (ADC) values on MRI (Figures 4C and D). Clinical symptoms resolved within a week, and a control MRI performed 3 weeks later showed the complete disappearance of the callosal lesion (Figures 4E-H).

MAIN POINTS

- The corpus callosum is a special region of the brain that is sensitive to trauma, drugs, and inflammatory processes due to the large number of excitatory amino acid receptors, cytokine receptors, and drug receptors it contains.
- Diffusion-weighted images and T2-weighted/fluid-attenuated inversion recovery magnetic resonance imaging sequences are crucial for diagnosis as they can identify cytotoxic lesions of the corpus callosum (CLOCCs), which lack a mass effect and do not enhance with contrast medium.
- Knowing the causes of CLOCCs and evaluating the patient with a clinical history will facilitate the radiologist in the differential diagnosis of conditions that have a similar appearance.

Case 4

A 26-year-old male patient who had bipolar disorder was admitted to the emergency department with a psychotic attack. At presentation, blood pressure was 160/90 mm Hg, and his pulse rate was 90 beats/min.He was under treatment with olanzapine and a brain MRI was performed to rule out organic causes. On MRI, there was a round hyperintense lesion on T2W and FLAIR sequences in the mid-splenium of CC (Figures 5A and B). The lesion showed restricted diffusion with a hyperintense signal on the DWI (C) and a hypointense signal on the ADC map (D). The patient's clinical condition was evaluated as olanzapine-induced mania. After sedation with a combination of lorazepam and haloperidol, he was referred to the psychiatric department to re-evaluate the use of olanzapine.

Case 5

A 24-year-old female patient developed blurred vision and diplopia while being followed up in the infectious diseases department with encephalitis. In cerebrospinal fluid analysis, no abnormal finding was detected except the low protein value (8 mg/dl). Then the patient underwent a brain MRI. On the MRI, although visual pathways, pituitary gland, and primary motor cortex were in normal appearance,

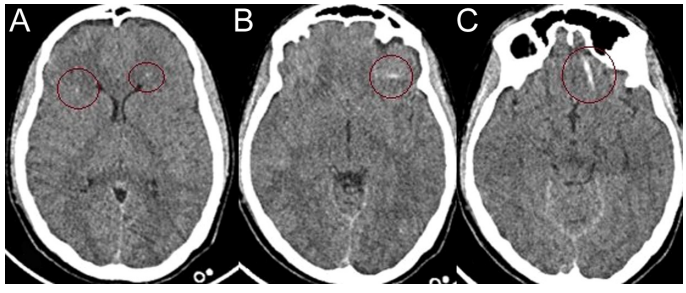

Figure 2. Subcortical linear hemorrhagic densities are shown in both frontal lobes on axial computed tomography images (A-C, circles).

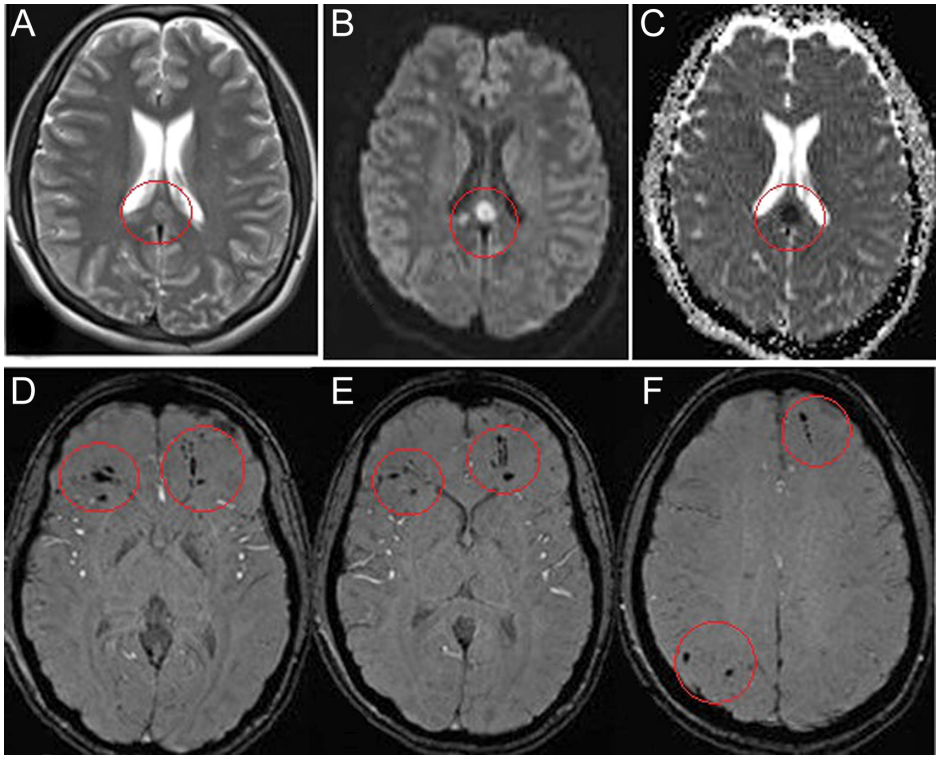

Figure 3. There is a round-shaped hyperintense focal lesion on the T2-weighted image (A, circle) in the mid-splenium of the corpus callosum with restricted diffusion, showing a hyperintense signal on the diffusion-weighted image (B, circle) and a hypointense signal on the apparent diffusion coefficient map (C, circle). SWI images (D-F, circles) show multiple hemorrhagic foci in periventricular and subcortical white matter.

there was a round-shaped lesion in the mid-splenium of the CC, which was hyperintense on T2W/FLAIR sequences (Figures 6A and B) and was accompanied by restricted diffusion on DWI images (Figures 6C and D). The MRI findings were consistent with CLOCCs. The patient received antibiotics (ceftriaxone and vancomycin) and supportive treatment. Her visual complaints improved within 72 hours following the therapy. Written informed consent was obtained from the patients who agreed to take part in the study.

DISCUSSION

CLOCCs take place in the literature with various expressions such as “mild encephalopathy with reversible splenial lesions (MERS),”

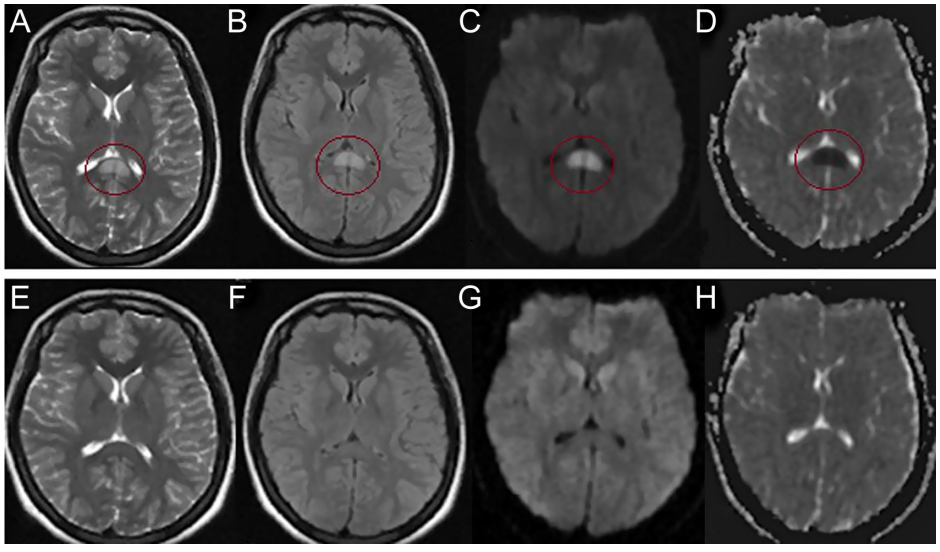

Figure 4. Magnetic resonance image reveals an oval-shaped T2-weighted/fluid-attenuated inversion recovery hyperintense focal lesion in the mid-splenium of the corpus callosum (A-B, circle) with restricted diffusion showing a hyperintense signal on diffusion-weighted imaging (C, circle) and a hypointense signal on the apparent diffusion coefficient map (D, circle). Third-week follow-up magnetic resonance imaging with T2-weighted imaging (E), fluid-attenuated inversion recovery (F), diffusion-weighted imaging (G), and apparent diffusion coefficient mapping (H) reveal the complete disappearance of the callosal lesion.

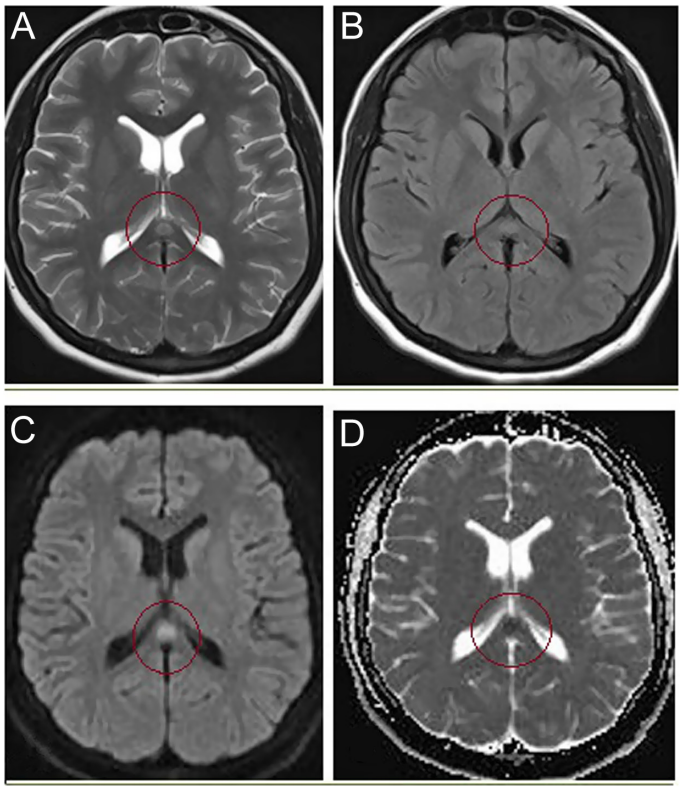

Figure 5. Magnetic resonance imaging shows a round lesion in the mid-splenium of the corpus callosum, which is hyperintense on T2-weighted (A, circle) and fluid-attenuated inversion recovery (B, circle) images. The lesion reveals restricted diffusion with a hyperintense signal on diffusion-weighted imaging (C, circle) and a hypointense signal on the apparent diffusion coefficient map (D, circle).

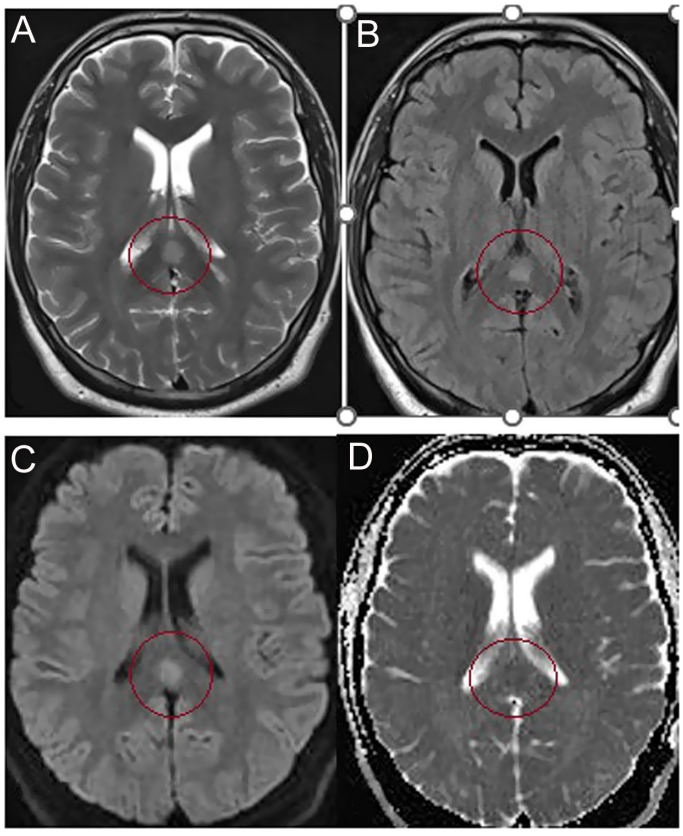

Figure 6. T2-weighted (A, circle) and fluid-attenuated inversion recovery (B, circle) axial images reveal a hyperintense round lesion in the splenium of the corpus callosum. The lesion shows restricted diffusion with a high signal on diffusion-weighted imaging (C, circle) and a low signal on the apparent diffusion coefficient (D, circle).

"reversible splenial lesion syndrome," and "clinically silent lesions in the splenium of the corpus callosum."[6-9] However, splenial lesions of the CC may not always be accompanied by encephalopathy and are not always completely reversible. It has been reported in the literature that restricted diffusion in the splenium of the CC can lead to gliosis.[11]

Recent studies have shown that these callosal lesions with significant diffusion restriction are caused by cytotoxic edema.[5] Trauma, infection, and inflammation activate macrophages and release inflammatory cytokines such as IL-1 and IL-6, initiating the cascade that leads to cytokinopathy. Interleukin 1-stimulated astrocytes secrete glutamate and increase its extracellular level by blocking its reuptake. With a stimulating effect on *N*-methyl-D-aspartate receptors, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors, sodium–potassium pumps, and aquaporins, glutamate causes the trapping of water molecules inside neurons.[5-7] This condition results in intracellular edema and restricted diffusion on ADC maps. The splenium of the CC is vulnerable to cytokinopathy. Compared with other brain areas, the neurons and oligodendrocytes of the corpus callosum have a higher density of cytokine receptors, glutamate and other excitatory amino acid receptors, and drug receptors.[10] Therefore, when cytokinopathy occurs, there is a tendency for cytotoxic edema to present in the splenium of the CC. In this case series, we reported 5 patients with different histories and conditions, each showing a similar lesion in the splenium of the CC.

The use of antiepileptic and antipsychotic drugs has an important role in the development of CLOCCs.[12] One of them is olanzapine, an atypical antipsychotic used by 1 patient in our series who had bipolar disorder. Kaino K. et al previously reported the pathophysiological mechanism of the splenial lesion resulting from the use of olanzapine for bipolar disease.[13] Olanzapine toxicity leads to intramyelinic edema and increased inflammatory cytokines; thus, hyperosmolar hyperglycemic state and neuroleptic malignant syndrome occur, which cause CLOCCs.

Although rare, CC lesions associated with postpartum late-onset preeclampsia have been reported in the literature.[14,15] As a result of hormonal and metabolic changes throughout pregnancy, vascular tone regulation may be affected during parturition and may lead to the formation of CLOCCs.[16] However, the pathogenesis of this condition is still not well understood.

It is crucial to differentiate CLOCCs from demyelination, infarction, posterior reversible encephalopathy syndrome (PRES), trauma, and tumors to avoid the wrong and unnecessary treatment. Each of these conditions tends to be asymmetric compared to CLOCCs, which are usually symmetric. Patients with multiple sclerosis typically have ovoid lesions perpendicular to the ventricular axis located in the pericallosal white matter. In PRES, the posterior circulation is typically affected, and MRI usually shows vasogenic edema in the bilateral parietooccipital

regions without restricted diffusion or pathological enhancement. Multifocal vasospasm segments in the anterior, middle, and posterior cerebral arteries on MRA images may be helpful in differentiating PRES syndrome from CLOCCs.[17] Entities including lymphoma and glioma may affect the same regions but show a more aggressive appearance with pathological contrast enhancement and vasogenic or infiltrative edema in the surrounding tissue. In addition, necrotic and hemorrhagic components are quite common in glioblastomas.

To summarize, the splenium of the CC is susceptible to trauma, infection, intracranial hypotension, and drug use due to the large number of receptors it contains. If there is a well-circumscribed, round, or oval-shaped isolated lesion in the splenium of the CC that restricts diffusion but does not enhance and is not accompanied by edema in the surrounding parenchyma, CLOCCs should be considered first in the differential diagnosis. In conclusion, knowing the clinical conditions that may lead to CLOCCs and being familiar with typical MRI findings are very important in making the differential diagnosis from other diseases and giving appropriate treatment.

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