Case Reports in Neurology

Case Rep Neurol 2023;15:113–119
DOI: 10.1159/000530944
Received: March 4, 2023
Accepted: April 24, 2023
Published online: June 12, 2023

Single Case – General Neurology

Cytotoxic Lesions beyond the Corpus Callosum Following Acute Meningoencephalitis and Mycoplasma Pneumoniae Infection: A Case Report and Literature Review

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Keywords
Cytotoxic lesions of the corpus callosum · Meningoencephalitis · *Mycoplasma pneumoniae* · Splenial lesion · Immunotherapy

Abstract
Cytotoxic lesions of the corpus callosum (CLOCCs) are secondary lesions associated with a variety of clinical causes. The presence of a small and reversible lesion in the splenium of corpus callosum with restricted diffusion on cranial magnetic resonance imaging is the defining feature. The clinical-radiological manifestations have been documented as mild and reversible. Severer presentations were scarcely reported. In this report, we described a 25-year-old man with preceding fever, worsening somnolence, and convulsions. He was diagnosed with acute meningoencephalitis and *Mycoplasma pneumoniae* infection after workups. After medical treatments, he had neurological deterioration and progressing CLOCCs from a small oval lesion in the center of splenium extending to the whole corpus callosum and bilaterally adjacent white matter. The patient received intravenous methylprednisolone and immunoglobulin successively, and his neurological conditions improved. The CLOCCs, not always mild and reversible, could present with severe clinicoradiological features.

Introduction

Neurological complications associated with immune-mediated injury triggered by prior infection are not rare and can involve both the peripheral and central nervous system. Examples of such complications affecting the peripheral nervous system include Guillain-

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Barré syndrome or critical-illness neuropathy, and the central nervous system such as acute disseminated encephalomyelitis (ADEM). In 2004, Tada et al. [1] first described 15 patients with clinically mild encephalitis or encephalopathy with a reversible splenial lesion as a new clinicoradiological syndrome, which was very different from ADEM. The clinical presentations were often mild and nonspecific, and almost all of the patients recovered within a short period of time [1]. The presence of an oval, isolated, and reversible lesion in the splenium of the corpus callosum (SCC) was the core radiological finding, with the characteristic feature of reversible diffusion restriction in magnetic resonance imaging (MRI) [1–3]. Recently, it was termed cytotoxic lesions of the corpus callosum (CLOCCs), which was proposed as a distinct disease entity based on the pathophysiologic hypothesis of the reversible lesions and the emphasis on the vulnerability of corpus callosum to excitotoxic injuries. It was previously known as mild encephalopathy with reversible splenial lesion (MERS) [4] or reversible splenial lesion syndrome (RESLES) [5, 6]. Almost all the reported cases had spontaneous total clinical and radiological recovery without treatments [1].

Here, we demonstrated a young adult developing an unusual course of severe CLOCCs, following an acute meningoencephalitis and *Mycoplasma pneumoniae* (*M. pneumoniae*) infection. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000530944).

Case Report

A 25-year-old previously healthy man was admitted to a local hospital for progressive hypersomnolence preceded by 1 week of fever and 2 days of headache. General convulsions developed the next day after admission, therefore, he was transferred to our hospital. On examination, his body temperature was 38.6°C, blood pressure 143/94 mm Hg, and he was in a stuporous status with prominent nuchal rigidity and bilateral rales on chest auscultation. His chest X-ray showed patchy consolidation over the right lower lung zone (shown in Fig. 1). The initial brain MRI showed prominent leptomeningeal enhancement at bilateral brainstem, cerebellum, and right cerebral sulci (shown in Fig. 2a, b) and a non-enhanced oval shape lesion at the SCC with increased signals in diffusion-weighted imaging (DWI), low signals in apparent diffusion coefficient (ADC), and hyperintensity in T2-weighted fluid-attenuated inversion recovery (T2-FLAIR) (shown in Fig. 3a–d). The cerebrospinal fluid (CSF) analysis revealed turbid appearance, significantly high pressure (420 mmH_2O), lymphocyte-predominant pleocytosis (white blood cells 148/μL, lymphocytes 95/μL), reduced glucose (43 mg/dL), and elevated protein (519 mg/dL). The biochemistry assay was all normal, including sodium, which was 136 mmol/L. The CSF pathogen studies were negative in bacteria, syphilis, fungus, tuberculosis, and virus via multiple polymerase chain reaction (FilmArray Meningitis/Encephalitis). The viral serology surveys including varicella zoster virus, herpes simplex virus, cytomegalovirus, and Japanese encephalitis virus were also negative. Serology detection for *M. pneumoniae* using rapid immunochromatographic test (Biocard™ *M. penunoniae* IgM kit, Labsystems Diagnostics, Finland) showed IgM positive at a titer of 1:320 (normal value <1:40) on the 2nd admission day, indicating an acute *M. pneumoniae* infection. Neither polymerase chain reaction analysis nor antibody detection of *M. pneumoniae* in the CSF was available in our hospital. He was treated with empirical antibiotics, antiviral agents, antiseizure medications, osmotic diuretics, and steroids. Resolution of the pneumonic patch was noted in the subsequent chest X-ray. The repeated CSF analysis 10 days later showed improvement, with a white cell count of 1/μL and a normal protein level at 13.2 mg/dL. However, his neurological condition deteriorated into a comatose

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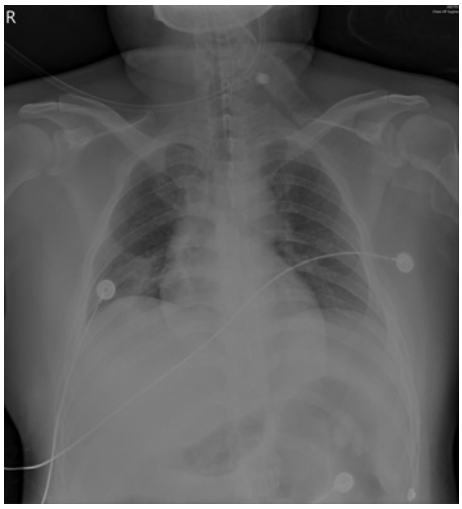

Fig. 1. On the first admission day, chest X-ray revealed patchy consolidation over right lower lung zone.

state with full-dilated unreactive pupils, flaccid quadriplegia, and ventilator support. The follow-up MRI 3 weeks after admission revealed apparent regression of the leptomeningeal inflammation (shown in Fig. 2c, d), but emergence of symmetric confluent hyperintensities on T2-weighted fluid-attenuated inversion recovery images involving the whole corpus callosum, bilateral internal capsules, and adjacent subcortical areas were without enhancement (shown in Fig. 3e–g). The extensive and symmetric white matter changes on the MRI did not conform to the typical findings in ADEM. Moreover, a nerve conduction velocity study disclosed severe amplitude reduction of compound muscle action potentials and mild reduction in sensory action potentials, compatible with a critical-illness polyneuropathy. Under the presumption of extensive inflammation affecting the central nervous system, we tried immunotherapies with intravenous methylprednisolone pulse therapy and intravenous immunoglobulin successively. His pupil responses recovered rapidly 2 days after completing the immunotherapies, and the consciousness and brainstem reflexes improved gradually within 2 weeks. The ventilator-support was weaned off successfully. The follow-up MRI on the 44th and the 79th admission day displayed continuing regression of the cytotoxic change in the corpus callosum and the white matter (shown in Fig. 3h–m). Three months after admission, he was discharged to a rehabilitation institution with clear consciousness and paraplegia. Six months after discharge, he could speak, eat, and move his upper limbs without efforts but still continued his rehabilitation for the moderate paraparesis.

Discussion

This reported young man was presented as acute meningoencephalitis with a concurrent *M. pneumoniae* infection. The initial brain MRI revealed typical leptomeningeal inflammation and a non-enhanced oval shape lesion in the center of SCC as a mild form of CLOCCs. The pneumonia and the CSF profile improved after empirical antibiotic therapy, but the neurological conditions deteriorated with impaired brainstem reflexes and flaccid quadriplegia. The follow-up brain MRI revealed regression of the leptomeningeal inflammation, the active lesions involving the entire corpus callosum, and the corticospinal tracts from subcortical to medial brainstem compatible with progressive cytotoxic changes of CLOCCs [2, 3]. Concomitant critical illness polyneuropathy was confirmed by electrophysiological examinations. Neurological complications from a complex immune-mediated mechanism following an acute meningoencephalitis and concurrent *M. pneumoniae* infection were strongly suspected.

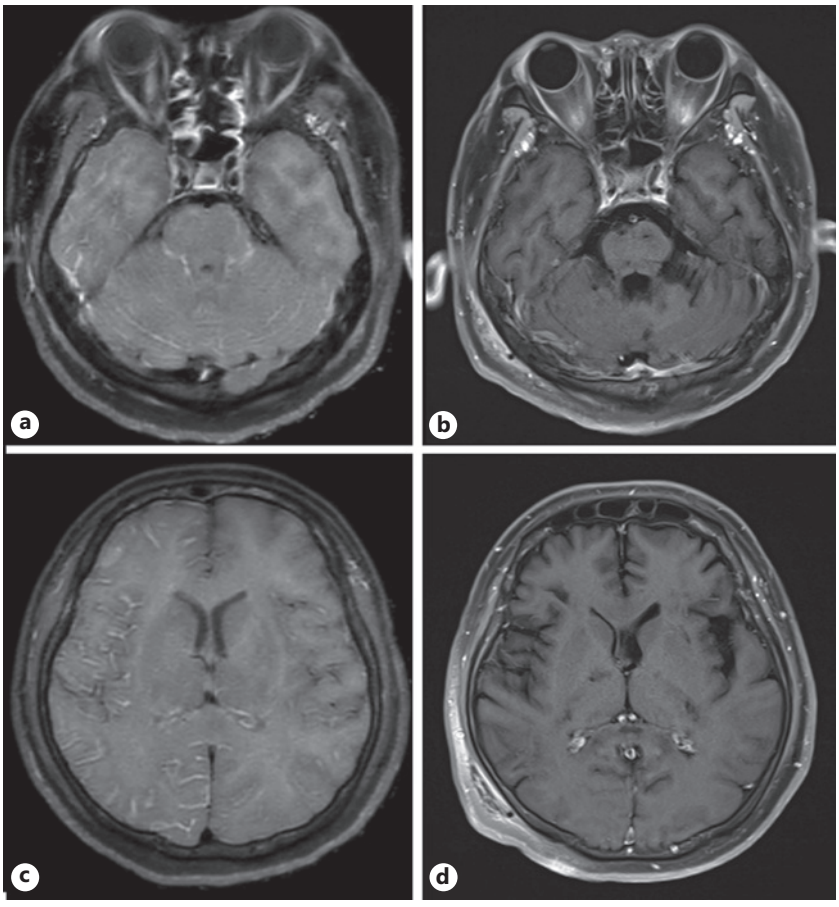

Fig. 2. a, **b** On the 2nd admission day, the post-gadolinium T1-weighted images revealed prominent leptomeningeal enhancement at bilateral brainstem, cerebellum, and right cerebral sulci. **c**, **d** On day 30, the post-gadolinium T1-weighted images with fat saturation revealed regression of the leptomeningeal inflammation and enhancement.

Among community-acquired pneumonia, *M. pneumoniae* is a common cause, and the neurological complications involving central or peripheral nervous system are not rare [7]. The pathogenesis of *M. pneumoniae*-associated neurological diseases is unclear; either direct invasion of the nervous system or immune-mediated inflammation has been assumed [7, 8]. Our patient's remarkable responses to immunotherapies might imply an underlying immunological pathophysiology.

Starkey et al. [3] has proposed the specific term of CLOCCs because these lesions are caused by cytotoxic edema associated with many diseases. The syndrome was first described by Tada et al. [1] in 2004 as a MERS. It is also named as "mild encephalopathy with reversible splenial lesions (MERS)" [9] and "reversible splenial lesion syndrome (RESLES)" [5, 6]. The clinical presentations and neuroradiological features are generally mild and reversible. Most SCC lesions are of oval or small round shape located in the center of splenium, and some may have symmetric extension to the anterior portions of corpus callosum and adjacent white matter [2, 3, 9]. These imaging variations are classified as MERS type 1 and 2, respectively [2, 9]. Cases with more extensive white matter involvement beyond the two types were rarely documented [2, 3]. One study analyzing ADC values in the corpus callosum of type 1 MERS has demonstrated that the pathology often extends beyond the lesions visualized with MRI [10]. The CLOCCs are regarded as secondary to a wide variety of clinical causes induced by

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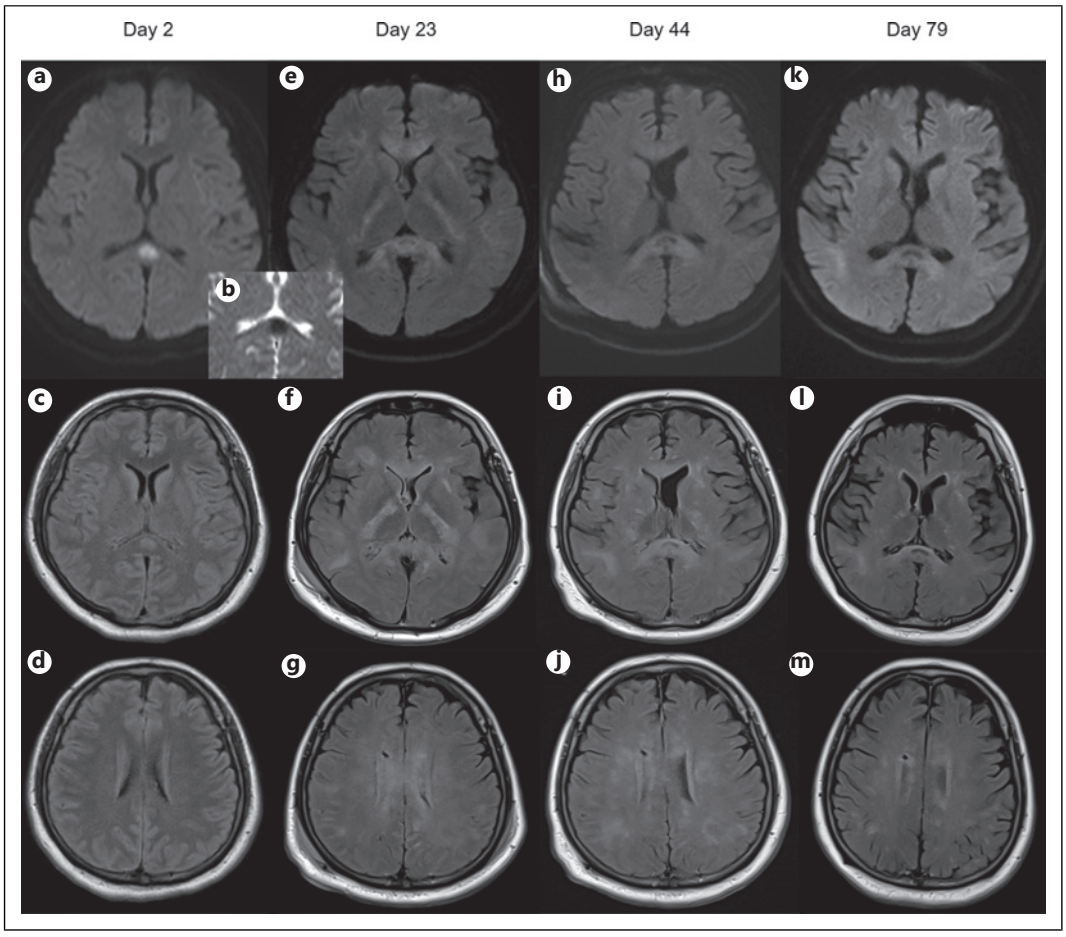

Fig. 3. On the 2nd admission day, MRI revealed one oval shape lesion in the center of splenium of corpus callosum with hyperintense signal on DWI and T2-FLAIR (**a**, **c**), low signal of ADC map (**b**), and no visible abnormality in the body of corpus callosum (**d**). On admission day 23, MRI showed extensive lesions involving the whole corpus callosum, bilateral internal capsules, and adjacent white matter with high signals on DWI (**e**) and T2-FLAIR (**f**, **g**). On 44th admission day, about 4 days after immunotherapy, MRI revealed slight regression of the high signals on DWI (**h**) and T2-FLAIR (**i**, **j**). On 79th admission day, MRI showed prominent regression of the high signals on DWI (**k**) and T2-FLAIR (**l**, **m**).

infection, trauma, metabolic disorder, malignancy, drug therapy, and others [1, 11]. Reported causative infections included influenza, mumps, Japanese B encephalitis virus, mycoplasma pneumonia, and the recent coronavirus disease 2019 (COVID-19) [12]. Since the concept of CLOCCs is well documented, more cases with CLOCCs have been reported recently [11, 12]. However, severe neurological presentations and extensive radiological features as in our case are scarcely reported [2].

Typical MRI features of CLOCCs are reversible signal intensity on T2-FLAIR and DWI, low ADC values, and without contrast enhancement [3, 5]. These lesions tend to be misdiagnosed as acute infarction because of the typical diffusion restriction on DWI and reduced ADC values. The underlying pathophysiology for the reversible changes has not been elucidated. Assumed hypotheses include intra-myelin cytotoxic edema from cytokinopathy and glutamate excitotoxicity [3, 5, 13, 14]. Corpus callosum is vulnerable to glutamate excitotoxicity because ample N-methyl-D-aspartate receptors are expressed in the myelin of corpus callosum [14]. It might be difficult to distinguish CLOCCs from ADEM, which is more common

clinically. The ADEM lesions are bilateral, asymmetrical, predominantly subcortical, or at deep white matter, and usually do not involve corpus callosum [15]. Most of the patients with ADEM develop severe neurological deficits within days. Neither the clinical course nor the MRI presentations of this presenting case conformed to the typical findings of the ADEM [1]. It is not unclear if there's overlapping pathogenesis between ADEM and CLOCCs with extensive white matter damage. In our experience in this case, the immunotherapy led to significant improvement in clinical symptoms even if the MRI lesions were not completely resolved. We speculated that complex mechanisms comprising inflammatory cytokinopathy and glutamate excitotoxicity underlie the severe form of CLOCCs [5, 14]. Immunotherapy hence may play an important role in the acute treatment of severe CLOCCs.

Severe CLOCCs could develop and progress after a meningoencephalitis and *M. pneumoniae* infection. Cranial MRI is important for the diagnosis and status tracking. Immunotherapy could improve the clinical and radiological outcomes in severe CLOCCs.

Statement of Ethics

This case report was reviewed and approved by the Institutional Review Board of the Chi Mei Medical Center, approval number (11110-E01). Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors received no specific funding for this work.

Author Contributions

Data curation, K.-H.L. and T.-C.W.; conceptualization, T.-C.W. and P.-S.Y.; validation and supervision, P.-S.Y.; writing – original draft preparation, K.-H.L. and P.-S.Y.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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