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A cerebral phenotype of chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids: A case report and review of the literature

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# **Abstract**

CLIPPERS (chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids) is an inflammatory central nervous system disorder that gives rise to brainstem symptoms such as diplopia and articulatory disorders. It shows characteristic "salt-and-pepper" enhancing brainstem lesions on magnetic resonance imaging (MRI) scans. We present an unusual case of CLIPPERS, in which a 29-year-old man initially presented with a seizure. Brain MRI

ACCEPTED MANUSCRIPT revealed faint open-ring enhancements in the right frontal lobe, and a brain biopsy was performed to

make a definitive diagnosis. Immunohistological tests showed perivascular infiltration by primarily

CD3- and CD20-positive cells, albeit including a few CD68-positive cells, which confirmed a

diagnosis of CLIPPERS. Both the symptoms and the MRI findings were markedly improved by 3

courses of steroid (methylprednisolone) pulse therapy, followed by oral steroid (prednisolone)

administration. This case shows that CLIPPERS can present as a phenotype of cortical lesions and

seizures as the first signs. A brain biopsy should therefore be actively carried out for differential

diagnosis, especially when other, cortically based inflammatory disorders are suspected.

Keywords: CLIPPERS, cerebral lesion, seizure, interleukin 6, pons, cortex

1. Introduction

CLIPPERS (chronic lymphocytic inflammation with pontine perivascular enhancement

responsive to steroids) was first publicly identified as a unique disorder by Pittock et al. (2010). It is

a rare inflammatory central nervous system (CNS) disorder with characteristic brainstem lesions.

Magnetic resonance imaging (MRI) scans of the brain show a punctate or curvilinear gadolinium

enhancement effect with a "salt-and-pepper" appearance, usually centered on the pons, and patients

experience facial sensory abnormalities, diplopia, ataxia, and dysarthria that are consistent with the

site of the lesion. However, there are a few reports of cases of CLIPPERS in which the lesions were

not restricted to the brainstem but were also found in the cerebral cortex. Such cases had signs and

symptoms corresponding to a cortical lesion location, including seizure (Lane et al., 2014). Notably,

no reports have presented a case in which the cerebral lesions occurred first and seizures were the

initial sign. We report the first known presentation of the latter phenotype, known as cerebral

CLIPPERS, in which the cerebral lesions and a seizure occurred before the pontine lesion. Because

of the unusual presentation, CLIPPERS in this case was diagnosed via brain biopsy.

2. Case Report

The patient was a 29-year-old left-handed man who experienced a seizure after drinking alcohol and

was then admitted to a nearby hospital. After the seizure had been treated, he continued to exhibit mildly disturbed consciousness (Glasgow Coma Scale [GCS]: E4V3M5), dysarthria, and left-arm paralysis. Therefore, he was initially diagnosed with non-convulsive status epilepticus. The immediate intravenous administration of levetiracetam (3000 mg) and fosphenytoin (750 mg) led to an improvement in his degree of consciousness (GCS: E4V5M6) and fewer sharp waves in a right superior frontal lesion as observed with electroencephalography (EEG). However, his left-arm paralysis remained, so he was transferred to our hospital.

In a physical examination on admission, he was alert but apathetic, had a fever of 38°C, and reported a headache. On the Japanese version of the Montreal Cognitive Assessment (MoCA-J), he had a score of 9/30, which indicates a disturbance of executive functions, attention, language, and memory. Moderate left-arm weakness was observed, with a left-side grip strength of 0 kg versus a right-side grip strength of 26 kg. He exhibited left-side-dominant hyperreflexia, a positive left-side Trömner and Hoffmann reflex, and an unstable gait. He did not exhibit sensory disturbances, cerebellar ataxia, or autonomic nervous system disturbances.

His blood cell count, hepatic and renal functions, and glucose tolerance were all normal, but his leukocyte count (16,600/μL) and C-reactive protein levels (1.35 mg/dL) were both elevated. Serum levels of angiotensin-converting enzyme (ACE; 8.8 IU/L) and sIL2R (395 U/mL) were normal, and an antibody panel was negative for antinuclear, anti-SS-A, anti-SS-B, MPO-ANCA, PR3-ANCA, and anti-AQP4 antibodies. Human leukocyte antigen typing was negative for B51 and B54. An analysis of cerebrospinal fluid (CSF) showed a high cell count (321/µL) comprised of polymorphonucleocytes (40%) and mononucleocytes (60%) and elevated protein levels (108 mg/dL). CSF levels of sugars (56 mg/dL) and myelin basic protein (< 31.3 pg/mL) were normal. Immunological activity in the CNS was revealed by an elevated immunoglobulin G index (0.85; normal: <0.7) and a positive test for oligoclonal bands. Moreover, a marked increase in CSF levels of interleukin-6 (IL-6; 2,710 pg/mL) suggested that specific inflammatory or immunological events had occurred in the CNS. Various viral tests, including polymerase chain reaction tests, were negative, as were tuberculosis and fungal culture tests. After we administered levetiracetam (3000

MACCEPTED MANUSCRIPT mg), EEG monitoring revealed frequent sharp waves in his right superior frontal lesion. However, a slow (5–6 Hz) theta wave was the major observation, and his basic rhythms had lower amplitudes in the right hemisphere.

T2-weighted brain MRI on the third day after onset showed a high-intensity lesion in the right frontal cortex that was faintly enhanced by gadolinium to reveal an open-ring shape (Fig. 1a), as well as lesions in the bilateral insula and right temporal lobe. No gadolinium-enhanced lesions were seen in the brainstem (Fig. 2). T2-weighted brain MRI on the 18th day after onset revealed new high-intensity lesions in the left globus pallidus, internal capsule, pulvinar nuclei, midbrain, pons, left cerebellar peduncle, and medulla oblongata in addition to the previous lesions. These new lesions were gadolinium-enhanced in T1-weighted images. In 3D fast spin echo T1-weighted images, the characteristic punctate and curvilinear patterns of enhancement were found in the new lesions in the thalamus, midbrain, and pons (Fig. 1b). Tests for ACE elevation in blood and CSF were negative, and a thoracoabdominal contrast computed tomography scan showed no noticeable tumors or obvious lymph node enlargement.

A brain biopsy of the right frontal lobe was performed at this point. Pathological examination of the specimen showed perivascular lymphocyte infiltration but no vasculitis, demyelination, or malignancies. Histological tests confirmed the perivascular lymphocytic infiltration. An immunohistological examination showed that ~60% of these lymphocytes were CD3-positive cells derived from T cell lymphocytes and that ~40% were CD20-positive cells derived from B cell lymphocytes. We also observed a few CD68-positive cells that were probably microglia or macrophages (Fig. 3). A malignant tumor, vasculitis, and sarcoidosis were ruled out, and given the punctate and curvilinear lesions noted in the midbrain and pons on MRI and the pathological findings from the brain biopsy, we definitively diagnosed CLIPPERS. Immediately after the brain biopsy, a 3-day course of steroid pulse therapy with methylprednisolone (1 mg/day) was prescribed. This was followed-up with oral prednisolone (55 mg/day; 1 mg/kg/day) as post-pulse therapy. Then, prednisolone was reduced at a rate of 5 mg every 2 weeks. After steroid treatment was initiated, his physical condition markedly improved within the first week. His MoCA-J score improved to 26/30

points, and he was able to walk. Furthermore, his left grip strength had improved to 32 kg. Faint high-intensity lesions in the left globus pallidus, bilateral pulvinar nuclei, midbrain, and medulla oblongata remained on T2-weighted or fluid-attenuated inversion recovery MRI images, but we observed no gadolinium enhancement (Fig. 2). The patient was discharged on a continuing oral prednisolone dose of 30 mg/day. Over 6 months of follow-up, we observed no clinical relapse or new abnormalities in brain MRI scans (Fig. 2).

### 3. Discussion

Pittock et al. (2010) described 8 cases of CLIPPERS and 4 key characteristics of the disorder: 1) the development of brainstem-related signs and symptoms such as facial sensory impairment, diplopia, cerebellar ataxia, and articulatory disorders; 2) gadolinium enhancement in brainstem, cerebellar, and/or spinal MRI scans with a "salt-and-pepper" pattern; 3) perivascular lymphocyte infiltration composed mainly of CD3- and CD20-positive cells, with a limited number of CD68-positive lymphocytes, and no accompanying demyelination or vasculitis; and 4) significant improvement with steroid therapy but the potential for recurrence with decreased steroid dosages.

Tobin et al. (2017) reexamined 35 patients diagnosed as CLIPPERS and divided them into 23 cases of CLIPPERS and 12 cases of non-CLIPPERS. Furthermore, they compared 23 cases of CLIPPERS and 12 cases of non-CLIPPERS and proposed differential diagnostic criteria for CLIPPERS based on clinical, radiological, and neuropathological findings. All of their criteria must be met for a diagnosis of 'definite CLIPPERS', and our case did not meet all of their clinical and radiological criteria. Specifically, the observation of a seizure, hemiparesis, and a ring-enhanced right frontal lobe lesion deviate from their criteria (Fig. 1). However, we think that these deviations from the typical CLIPPERS presentation are characteristics indicative of cerebral CLIPPERS.

Previously reported atypical cases of CLIPPERS included such findings as steroid resistance, the absence of typical brainstem findings, rapid (i.e., within several days) progression of severe neurological disorders, fever and nocturnal sweating with weight loss, seizures in the early stages, disturbed consciousness, brain edema or focal edema surrounding lesions, and ring-enhanced lesions (Zalewski and Tobin, 2017).

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The case presented herein is the first case of atypical CLIPPERS manifesting with a seizure and a cortical lesion before any brainstem lesion or related signs appeared. Brainstem lesions developed first in nearly all reported cases of CLIPPERS, with cerebral lesions identified later, after the diagnosis of CLIPPERS (Taieb et al., 2012, Lane et al., 2014). Although the cerebral lesions in CLIPPERS resulted in seizures in several cases (Lane et al., 2014), these again followed, rather than preceded, the signs resulting from brainstem lesions.

Pleocytosis and increased CSF IL-6 levels can also be atypical signs of CLIPPERS. However, there have been no reported cases with pleocytosis in the CSF as high as 321/µL (Zalewski and Tobin, 2017), as was found in the present case. In addition, CSF IL-6 levels are a somewhat nonspecific marker, with IL-6 levels of ≥1000 pg/mL being common in optic neuromyelitis, malignant tumors, and inflammatory CNS disorders such as Behçet's disease and meningitis, but there are no reports specifically correlating CLIPPERS and elevated CSF IL-6 levels (Uzawa et al., 2017). In cases with high CSF IL-6 levels, diagnostic considerations should include the possible presence of other conditions and the possibility of it being an epiphenomenon secondary to CNS tissue damage. Future studies will be required to determine if a high CSF IL-6 level can be a marker for diagnosing cerebral CLIPPERS.

In terms of treatment, high-dose steroid pulse therapy is still the first choice, and post-pulse treatment by prednisolone (1 mg/kg/day) is recommended. Recurrence has resulted from decreasing the steroid dose, so skillful management and slow tapering are necessary. In the case of prednisolone, there is a report that recurrence is suppressed by a maintenance dose of 20 mg/day and upwards (Taieb et al., 2012). There are also reports that the concomitant use of an immunosuppressant such as azathioprine when decreasing the dose can prevent a relapse (Lane et al., 2014). Indeed, such a protocol may well be necessary in the future management of our patient.

## 4. Conclusion

We have reported a case of CLIPPERS that initially featured a seizure and a cerebral lesion and only manifested typical brainstem MRI findings later in the disease progression. The definitive diagnosis of CLIPPERS was based on brain biopsy findings. Clinicians should therefore consider

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atypical CLIPPERS as a differential diagnosis in cases of seizures and cerebral lesions on MRI scans, and actively biopsy the cerebral lesion.

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## **Declarations of interest**

none.

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# **Figure Legends**

Figure 1a. Brain MRI image on the third day after onset. (A) Axial gadolinium-enhanced T1-weighted images revealed a tumor-like lesion measuring 2 cm in maximum diameter and an open-ring enhancement in the right frontal lobe. (B) DWI after a seizure showed an increased signal in the cerebral cortex of the right hemisphere. (C) The tumor-like lesion with a surrounding slightly increased DWI signal appeared as a zone of high ADC intensity and resembled a vasogenic edema. Figure 1b. Brain MRI image on the 18th day after onset. (D) Axial T2-weighted MRI showed a high-intensity enlarging tumor-like lesion with perifocal edema in the right frontal lobe. Axial (E, F, G) gadolinium-enhanced black-blood T1-weighted fast spin-echo MRI before biopsy revealed

ACCEPTED MANUSCRIPT extensive multiple punctate or curvilinear enhancement lesions within the thalamus, midbrain, pons, and medulla oblongata. Abbreviations: ADC, apparent diffusion coefficient; DWI, diffusion-weighted imaging; MRI, magnetic resonance imaging

Figure 2. Transitional change in the brainstem lesions in gadolinium-enhanced MRI images. Upper: T1-weighted gadolinium-enhanced MRI. Lower: Gadolinium-enhanced black-blood T1-weighted fast spin-echo MRI. Far left: There was no lesion in the MRI scan on the third day after onset. Middle left: Multiple curvilinear, punctate, or patchy lesions in the midbrain and pons were visible in the gadolinium-enhanced MRI scan on the 18th day after onset. Middle right: The enhanced lesions disappeared after steroid pulse therapy. Far right: Six months after discharge, no new lesions, including gadolinium enhanced lesions, had appeared. Abbreviations: MRI, magnetic resonance imaging

Figure 3. Brain histopathology images of the brain biopsy specimen. HE staining revealed lymphocytic infiltration in the perivascular spaces. CD3- and CD20-positive B cells were predominant in the perivascular cluster of lymphocytes. A few CD68-positive histiocytes were found in infiltrating inflammatory cells. Abbreviations: HE, hematoxylin and eosin V.C.C.C.C.

Fig.1a

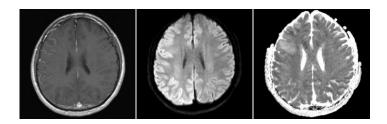
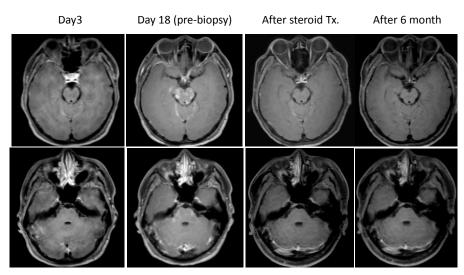


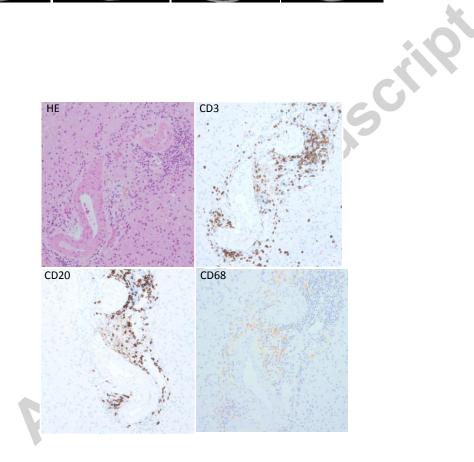
Fig.1b

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Fig.2







# Highlights

- This was an atypical cerebral-type case of CLIPPERS with no early brainstem findings
- Initial tests showed enhancing cortical lesions in MR images and seizure
- Atypical CLIPPERS can have cortical symptoms but usually after brainstem lesions

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Atypical CLIPPERS should be included in the differential diagnosis

