

Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) with intracranial Epstein–Barr virus infection

A Case Report

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Abstract

Background: Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) is an inflammatory disorder in the central nervous system (CNS) with distinct clinical, radiological, and pathological features. The pathophysiology of CLIPPERS still remains unclear and the reports are quite few. Although the radiological lesions were reported to be located predominantly in the pons, brachium pontis, and cerebellum, other adjacent structures such as the white matter and spinal cord were very recently reported as involved regions in CLIPPERS. In this study, we report a case of CLIPPERS presenting with intracranial Epstein–Barr virus (EBV) infection and diffuse white matter involvement.

Case summary: A 37-year-old male was diagnosed with mediastinal Hodgkin's lymphoma (lymphocyte predominance type) at the age of 26, and then obtained complete remission after treatment and remained free of relapse for 11 years. He was admitted with 7 months' history of mental disorder, and 20 days' history of gait and limb ataxia, dysphagia, and cough. The diagnosis of CLIPPERS was established based on the findings of punctate and nodular enhancing lesions in the bilateral pons, the basal ganglia, the mid-brain, the pontine brachium, and diffuse white matter in magnetic resonance imaging (MRI), together with CD3⁺ T-lymphocytic inflammatory infiltration in perivascular and parenchymal area revealed by bilateral parietal lobe brain biopsy. Also, our patient exhibited a good response to steroid therapy and remained free of relapse for 5 months. Importantly, we found intracranial Epstein–Barr virus infection in this patient.

Conclusion: CLIPPERS might be an autoimmune disorder, and intracranial EBV-infection raises the possibility that EBV-associated autoimmunity is associated with CLIPPERS pathogenesis.

Abbreviations: CAEBV = Chronic Active EBV disease, CLIPPERS = chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids, CNS = central nervous system, CSF = cerebrospinal fluid, EBNA = Epstein–Barr nuclear antigens, EBV = Epstein–Barr virus, EBVCA = Epstein–Barr viral capsid antigen, MRI = magnetic resonance imaging.

Keywords: autoimmune disorder, CLIPPERS, Epstein–Barr Virus, lymphoma, steroids

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1. Introduction

Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) is a recently defined immune-mediated and treatable central nervous system (CNS) inflammatory disease with distinct clinical, radiological, and pathological characteristics.^[1–3] CLIPPERS patients present with a favorable but dependent response to steroids therapy and show a punctate and nodular pattern of gadolinium enhancement “peppering” in the pons, brainstem, white matter, and other adjacent structures. White matter perivascular lymphocytic infiltration with or without parenchymal extension is another striking characteristic. Several studies suggested that CLIPPERS is an autoimmune disorder, but the related evidence still remains deficient.^[1,4] Now, we report a case of CLIPPERS patient confirmed by clinical, radiological, and pathological characteristics. Interestingly, a significantly elevated load of Epstein–Barr virus (EBV) DNA was detected in his cerebrospinal fluid (CSF). This presentation raises the possibility that EBV-associated immunity dysfunction may be related to the pathogenesis of CLIPPERS. As far as we perceive, this is the first case of CLIPPERS with CNS EBV infection.

2. Case report

A 37-year-old male was diagnosed with mediastinal Hodgkin's lymphoma (lymphocyte predominance type) at the age of 26. After treated with ABVD (Adriamycin, Bleomycin, Vinblastine, Dacarbazine), he obtained complete remission and remained free of relapse for 11 years. Seven months prior to admission, he described sadness when feeling tough in his career. Meanwhile, with the irritability, apnea, and reduction of speech, he found the unwillingness of communication with others. After treated with escitalopram oxalate, risperidone, and sertraline, he gradually emerged symptoms of mania, which is characterized by increased grandiloquent speech and less need for sleep. Diagnosed with bipolar disorder at the local hospital, he was given VPA-Mg, buspirone and clonazepam, and then obtained an improvement. One month ago, he subacutely developed gait and limb ataxia featured by unstable walking and clumsy hand movements. Dysphagia, cough, and dysarthria appeared afterwards. He also had a generalized seizure (Tonic) 2 weeks before admission, and then developed headache, shortness of breath, and somnolence.

On admission, the patient's temperature was normal. Neurological examination revealed the right abducens nerve palsy and limited left eyeball movement to any direction. Appearance of hoarseness, dysphagia, and cough had been noticed, with apparent pharyngeal reflex decreased. Deep tendon reflexes were obviously increased. Bilateral Hoffmann sign, Babinski sign, and Chaddock sign were positive. Muscle strength scores of bilateral upper and lower limbs were 4 on the Medical Research Council scale. The rest of the neurological examinations were normal. The leukocytoclastic vasculitis was excluded because no palpable purpura, urticarial plaques, vesicles, bullae, or pustule was noted, nor were signs of joints injury or gastrointestinal injury.^[5] Fever, malaise, weight loss, arthralgias, and myalgias were not detected in this case. Hematuria and proteinuria were absent in this case. Nor was any suspicious pulmonary hemorrhage noted. Thus, the ANCA vasculitis was also excluded.^[6]

Laboratory investigations revealed that the patient had normal complete and differential blood count, sedimentation rate, C-reactive protein, thyroid hormone, renal and liver function. Serum immunological study, antinuclear antibodies, double-stranded DNA antibodies, and antibodies against extractable nuclear antigens were all negative. Paraneoplastic autoantibodies panels including anti-Hu, anti-CV2, anti-Ma2, anti-Ri and anti-voltage-gated K channels were negative. NMDA IgG, AMPA1 IgG, AMPA2 IgG, LGI1 IgG, CASPR2 IgG, and GABA B receptor IgG were all negative. Systemic workup for malignancy markers was also negative. Serum IgG and/or IgM of *human immunodeficiency virus*, *hepatitis B virus*, syphilis, and *herpes simplex virus* were all negative. However, the patient serum was positive for Epstein-Barr nuclear antigens (EBNAs) antibody and Epstein-Barr viral capsid antigen IgG (EBVCA-IgG >22RU/ml) but negative for Epstein-Barr viral capsid antigen IgM (EBVCA-IgM >22RU/ml), suggesting a possible history of EBV infection. The level of EBV DNA in the blood (<5000 copies) was also specified to rule out Chronic Active EBV disease (CAEBV) in this young patient. CSF examination revealed mildly elevated protein levels (1.3 g/L, normal 0.15–0.40 g/L) and lymphocytic pleocytosis (108/mm³, normal <3/mm³). Notably, an elevated load of EBV-DNA was detected in CSF by PCR as 2.01×10^4 copies (normal <5000 copies).

Brain magnetic resonance imaging (MRI) showed hyperintense signal on T2-weighted images, associated with patchy gadolinium enhancement on T1-weighted images in the bilateral pons, the

basal ganglia, the midbrain, the pontine brachium, and diffuse white matter (Fig. 1A1, A2). The clinical and MRI findings could suggest other disorders, such as neurosarcoidosis, CNS vasculitis, autoimmune encephalitis, histiocytosis and paraneoplastic disease. These differential diagnoses can be excluded by extensive evaluations and the previously reported cases.^[1] Bilateral parietal lobe brain biopsy revealed lymphocytic inflammatory infiltration in perivascular and parenchymal area (Fig. 1C), consisting primarily of CD3⁺ T lymphocytes (Fig. 1D) and few detected CD1a⁺ cells, CD30⁺ cells, CD10⁺ cells and CD20⁺ cells. All infiltrated cells were negative for CD56, CD99, TDT, or CD14. The proliferation rates, as detected by Ki67 antigen immunohistochemistry was ~10% (Fig. 1E). Neuropathology lacked characteristic microglial nodules or neuronophagia. No demyelination, granulomatous inflammatory, or necrotizing vasculitis was observed.

As intravenous dexamethasone (15 mg daily) was initiated, the patient responded well with gradually improved symptoms within a week from starting treatment, despite mild persistent mental abnormality and dysphagia. CSF analysis results also showed a decrease of the cytology (white blood cells: 47/mm³, 99% lymphocytes). The pontine lesions in MRI decreased in numbers and extent 3 weeks from starting treatment (Fig. 1B1, B2). Four weeks later, the dexamethasone was tapered by 5 mg every 5 days until discontinuance. Oral prednisolone (30 mg daily) was therefore initiated, ultimately maintained at 5 mg daily after sequential tapering. During the 5 months of steroids therapy, the clinical and radiological remission was maintained.

3. Discussion

The patient was admitted with 7 months' history of mental disorder, 20 days' history of gait and limb ataxia, dysphagia, and cough. The MRI images and histopathological features, along with the favorable clinical and radiological responses to corticosteroids led us to consider the diagnosis of CLIPPERS. However, the specialty in our patient should be noted: (i) this patient has a history of mediastinal Hodgkin's lymphoma (lymphocyte predominance type), and after treated with ABVD (Adriamycin, Bleomycin, Vinblastine, Dacarbazine), he obtained complete remission and remained free of relapse for 11 years; (ii) this is the first study reporting a CLIPPERS patient with an elevated load of EBV-DNA in the CSF; (iii) this patient's MRI showed lesions of broad areas of cerebral white matter.

Although recurrence of Hodgkin's lymphoma in the brain is rarely reported, we did consider the possibility of newly emerged CNS lymphoma occurring after treatment for Hodgkin's lymphoma because of the immunosuppression.^[7] However, findings in brain biopsy showed no evidence of CNS lymphoma since the Ki67 labeling index, which is strictly associated with cell proliferation, was 10%. Manual CSF cytology and hematologic investigations did not reveal any malignant cells either. In addition, the patient did not suffer from suspicious fever or body weight loss. Nor was lymphadenopathy found. Thus, we intended to diagnose the patient with CLIPPERS for now. Still, it remains to be elucidated whether CLIPPERS is associated with CNS lymphoma. Some of the reported patients initially diagnosed with CLIPPERS finally progressed to CNS lymphoma despite receiving timely treatment in literatures. These patients responded well to steroids therapy at first and gained symptoms improvement with decreased lesions. However, long-term follow-up revealed worsened symptoms and re-emerged lesions in MRI, consequently leading to a second brain biopsy which

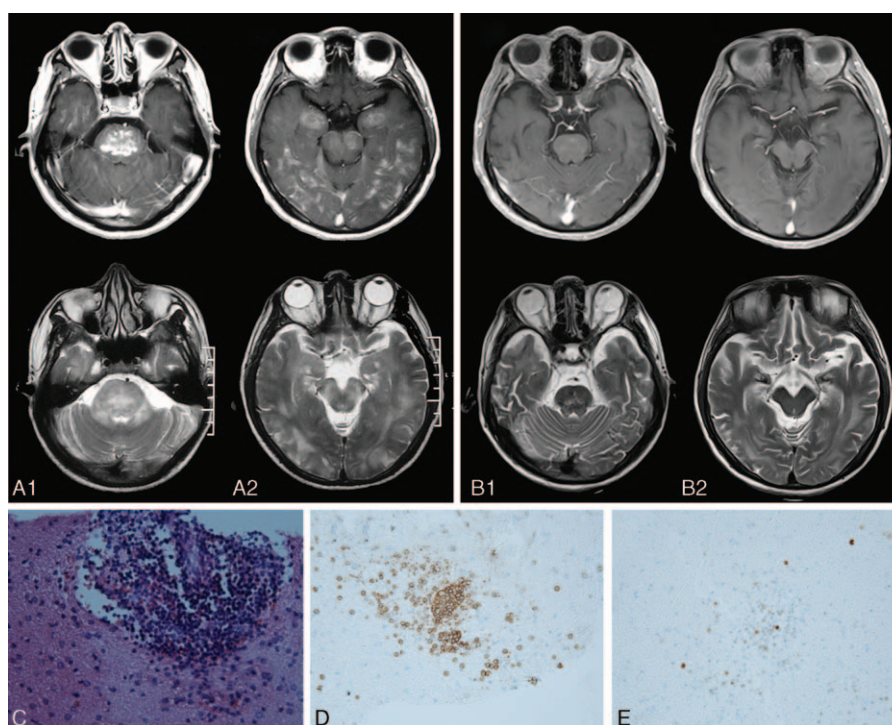


Figure 1. Neuroradiological images on admission and 3 weeks after steroid therapy and pathological findings from brain biopsy. Representative T1-weighted imaging with gadolinium enhancement (top row) and corresponding T2-weighted imaging (bottom row) on cervical MRI demonstrate changes of MRI features after steroid therapy. The images performed on admission show punctate and nodular enhancing lesions in the bilateral pons, the basal ganglia, the midbrain, the pontine brachium, and extensively in cerebral white matter, with a perivascular enhancement pattern (A1, A2). A decrease in the number and extent of pathology is observed on a cervical MRI scan after steroid treatment (B1, B2). In pathology findings from the parietal lobe specimen, hematoxylin and eosin staining showed lymphocytic inflammatory infiltration with perivascular and parenchymal cells (C; $\times 100$). The lymphocytic infiltrates were mainly composed of CD3⁺ T lymphocytes (D; $\times 100$). Proliferation rate, detected by Ki67 antigen immunohistochemistry, was about 10% (E; $\times 100$). MRI = magnetic resonance imaging.

gave the confirmed diagnosis of CNS lymphoma.^[8–10] Therefore, a long-term follow-up is necessary, aiming at monitoring the possible changes of symptoms or MRI features to confirm whether there is coexisting or subsequent development of CNS lymphoma. At the same time, a second biopsy is recommended if it is necessary, especially when worsening of clinical or radiological presentation appears in spite of proper immunosuppressive treatment, or when the immunosuppressive therapy is refractory.

The exact pathogenesis of CLIPPERS remains largely unknown. Previous investigators proposed that CLIPPERS might be an autoimmune disorder due to the clinical response to immunosuppressive therapies, and the inflammatory infiltration around perivascular regions, where the possible targeted autoantigen is located.^[1] However, this hypothesis is incomplete because the specific mechanism is still unclear. In this CLIPPERS patient, a great attention should be paid to the early elevated load of EBV-DNA in CSF as well as the possible history of EBV infection. Several autoimmune diseases, including multiple sclerosis, systemic lupus erythematosus, and Sjögren's syndrome, are associated with EBV infection. EBV causes autoimmune reaction through molecular mimicry, epitope spreading, and suppression of TLRs.^[11] We hypothesize that the CLIPPERS may involve an autoimmune process. Growing evidence suggests that some of the EBV-encoded latent proteins, such as the EBNA, share linear and functional sequences identity with host proteins such as neuronal protein α -synuclein. During acute or persistent reactivating infection, EBV can produce pro-inflammatory signals which promote anti-viral responses and cause tolerance abandon of immune system with mimicry to α -synuclein, leading

to the oligomerization of α -synuclein.^[12] Besides the main expression in neurons, α -synuclein is also expressed in cerebral blood vessels,^[13] around where is exactly the place of inflammatory infiltration in CLIPPERS. Thus, we propose a possible mechanism that the autoimmune response induced by EBV infection might be one of the possible pathological causes of CLIPPERS, contributing to the autoimmune hypothesis.

The high load of EBV DNA in the CSF but not in the blood suggests that the affected cells are resident to the CNS rather than recruited from the periphery. It is reported that the main target cells of EBV are epithelial cells and B cells.^[14] EBV could infect epithelial cells via apical to basolateral transcytosis.^[15] Thus, the elevated EBV DNA in CSF may be due to the CNS EBV reactivation or the activated resident EBV-positive cells in the CNS by the local inflammation.

The manifestation of bipolar disorder may be attributable to lesions of broad areas of cerebral white matter, which may also cause seizure-like activity at the early stage of the disease. Although the reported lesions were located predominantly in the pons, brachium pontis, and cerebellum, a recent study showed that diffuse white matter might be involved in CLIPPERS as well.^[16] Close attention should be paid to the clinical manifestations of lesions in other cerebral regions.

4. Conclusion

This is the first study reporting a CLIPPERS case with an elevated load of EBV-DNA in the CSF. Our findings indicate that intracranial EBV infection may be associated with the pathogenesis of CLIPPERS through autoimmunity. In addition, as it

remains undetermined whether CLIPPERS is an independent disease entity or syndrome or a presage of other diseases, long-term follow-up of CLIPPERS patients, especially those who have a history of Hodgkin's lymphoma, is highly recommended.

References

- [1] Pittock SJ, Debruyne J, Krecke KN, et al. Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS). *Brain* 2010;133:2626–34.
- [2] List J, Lesemann A, Wiener E, et al. A new case of chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids. *Brain* 2011;134:e185.
- [3] Simon NG, Parratt JD, Barnett MH, et al. Expanding the clinical, radiological and neuropathological phenotype of chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS). *J Neurol Neurosurg Psychiatry* 2011;83:15–22.
- [4] Kira J. The expanding phenotype of CLIPPERS: is it a disease or a syndrome? *J Neurol Neurosurg Psychiatry* 2012;83:2–3.
- [5] Jennette JC, Falk RJ. Small-vessel vasculitis. *N Engl J Med* 1997;337:1512–23.
- [6] Falk RJ, Jennette JC. ANCA small-vessel vasculitis. *J Am Soc Nephrol* 1997;8:314–22.
- [7] Mashima K, Suzuki S, Mori T, et al. Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) after treatment for Hodgkin's lymphoma. *Int J Hematol* 2015;102:709–12.
- [8] De Graaff HJ, Wattjes MP, Rozemuller-Kwakkel AJ, et al. Fatal B-cell lymphoma following chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids. *JAMA Neurol* 2013;70:915–8.
- [9] Lin AW, Das S, Fraser JA, et al. Emergence of primary CNS lymphoma in a patient with findings of CLIPPERS. *Can J Neurol Sci* 2014;41:528–9.
- [10] Taieb G, Uro-Coste E, Clanet M, et al. A central nervous system B-cell lymphoma arising two years after initial diagnosis of CLIPPERS. *J Neurol Sci* 2014;344:224–6.
- [11] Middeldorp JM. Epstein-Barr virus-specific humoral immune responses in health and disease. *Curr Top Microbiol Immunol* 2015;391:289–323.
- [12] Woulfe JM, Gray MT, Gray DA, et al. Hypothesis: a role for EBV-induced molecular mimicry in Parkinson's disease. *Parkinsonism Relat D* 2014;20:685–94.
- [13] Kim KS, Park JY, Jou I, et al. Regulation of Weibel-Palade body exocytosis by alpha-synuclein in endothelial cells. *J Biol Chem* 2010;285:21416–25.
- [14] Lunemann A, Rowe M, Nadal D. Innate immune recognition of EBV. *Curr Top Microbiol Immunol* 2015;391:265–87.
- [15] Tugizov SM, Herrera R, Palefsky JM. Epstein-Barr virus transcytosis through polarized oral epithelial cells. *J Virol* 2013;87:8179–94.
- [16] Taieb G, Labauge P, Ding MP, et al. CLIPPERS with diffuse white matter and longitudinally extensive spinal cord involvement. *Neurology* 2016;86:2216–7.