Introduction

Epstein-Barr virus (EBV) is known to cause encephalitis by initial infection or reactivation [1]. EBV encephalitis often occurs in childhood, but in adults, it mostly develops in those with immunological dysfunction [2]. However, a few adult-onset cases without immunological...
dysfunction have been reported [2–4]. In the treatment of EBV encephalitis, immunotherapy, such as steroid and intravenous immunoglobulin (IVIg), acyclovir, and ganciclovir are often used. However, the efficacy of the agents remains to be identified. Herein, we report a case of EBV encephalitis with gadolinium-enhanced punctate lesions, in which immunotherapy was effective.

**Case Report**

An 82-year-old man became mute in August 2020. The next morning, he was unre sponsive and had a fever of 39.7°C, so he was brought to our hospital. After admission, he was treated with meropenem (MEPM). His level of consciousness improved slightly, but the improvement was not sufficient. He was referred to our department on day 5.

His body temperature was 38°C. His Glasgow Coma Scale was E3, V2, M5. There were no other abnormalities in his vital signs. He had nuchal rigidity. Blood test revealed an increased white blood cell count of 13,330/µL (reference value is 3,900–9,800/µL) and an increased C-reactive protein of 3.84 mg/dL (reference value is less than 0.14 mg/dL). There were no abnormalities in liver enzymes and renal function. Hemoglobin A1c was 6.9% (reference value is 4.6–6.2%). Autoantibodies including antineutrophil cytoplasmic antibodies were negative. Angiotensin-converting enzyme was not elevated (5.3 U/L, reference value is 8.3–21.4 U/L). Cerebrospinal fluid (CSF) revealed a cell count of 169/µL (reference value is less than 5/µL) with monocytic predominance, an elevated protein level of 123 mg/dL (reference value is 15–45 mg/dL), a normal glucose level of 56 mg/dL (reference value is 50–75 mg/dL), blood glucose level was 169 mg/dL, a normal myelin basic protein (MBP) of 47.4 pg/mL (reference value is less than 102.0 pg/mL), and an elevated IgG index of 1.441 (reference value is less than 0.73). CSF cytology revealed no malignancy. Anti-N-methyl-D-aspartate receptor antibody in CSF was negative. Microbiological test for CSF was negative. Chest and abdominal computed tomography showed no malignant lesions or lymphadenopathy.

Since his consciousness had slightly improved after the initiation of MEPM, bacterial meningitis could not be ruled out, and MEPM 6 g/day and vancomycin 2 g/day were started on day 5. On the following day, his consciousness worsened, and magnetic resonance imaging (MRI) was performed. MRI showed diffusion-weighted imaging, fluid-attenuated inversion recovery (FLAIR), and apparent diffusion coefficient (ADC) high signals in the bilateral limbic regions and bilateral basal ganglia (Fig. 1a–d). Acyclovir 1,500 mg/day was added on the same day. On day 9, gadolinium-enhanced MRI showed punctate lesions in the bilateral basal ganglia (Fig. 1e, f). T2*-weighted imaging revealed no hemorrhagic lesions in basal ganglia (not shown). CSF cell count decreased to 67/µL; however, level of consciousness did not improve. Intravenous methylprednisolone was started on the same day. On day 17, EBV polymerase chain reaction was found to be positive in the CSF (300 copies/mL, reference value is less than 200 copies/mL), so we diagnosed EBV encephalitis. Polymerase chain reaction for herpes simplex virus, varicella-zoster virus, and human herpesvirus 6 in CSF were negative. Blood analysis showed that EBV viral capsid antigen IgG was positive, EBV viral capsid antigen IgM was negative, and EBV nuclear antibody was positive. His motor response slightly improved, but the improvement was not sufficient, so IVIg was initiated on day 20. On day 25, gadolinium-enhanced MRI showed reduction of punctate-enhanced lesions (Fig. 2a). He could speak on day 39, but he had difficulty eating. On day 46, gadolinium-enhanced MRI showed residual enhanced lesions (Fig. 2b). Intravenous methylprednisolone was added for 3 days on day 58 (Fig. 3). On day 68, he could eat, and the enhanced lesions disappeared (Fig. 2c). There was no recurrence of symptoms or enhanced lesions, and he was discharged to a nursing facility on day 180.
Discussion/Conclusion

EBV encephalitis is characterized by FLAIR-high signals in the bilateral basal ganglia or bilateral thalami on MRI [5]. This case was consistent with EBV encephalitis in that it showed FLAIR-high signals in the bilateral basal ganglia. On the other hand, a unique finding was that MRI showed gadolinium-enhanced punctate lesions like chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERs), which...
disappeared after immunotherapy. CLIPPERS is thought to be an inflammatory central nervous system disease, which a previous study reported was responsive to steroid and showed punctate enhancement in pons, cerebellum, and sometimes in basal ganglia [6]. The gadolinium-enhanced punctate lesions in our case were similar to CLIPPERS. No other encephalitis was reported to present with gadolinium-enhanced punctate lesions in basal ganglia. Vasculitis, demyelination, and lymphoma were considered as differential diagnoses. However, CSF cytology showed no malignancy, and the patient responded to immunotherapy without recurrence. CSF cytology and the clinical course lowered the possibility of lymphoma. Furthermore, demyelination was also less likely because of negative MBP in the acute phase.

There were a few reports of EBV encephalitis with vasculitis (Table 1) [4, 7]. In the present case, MRI showed ADC-high signal in basal ganglia. In central nervous system vasculitis, ADC-high signal reflecting vasogenic edema has been reported [8]. Furthermore, in a previous case of EBV encephalitis, perivascular lymphocytic infiltration mainly consisting of CD3 + and CD8 + T cells was reported [7]. In CLIPPERS, perivascular lymphocytic infiltration consisting mainly of CD3 + T cells is also characteristic [6]. Hence, the punctate enhancement like CLIPPERS in our case may also reflect perivascular lymphocytic infiltration.

EBV encephalitis often shows a self-limiting clinical course, while fatal cases were reported. Although acyclovir and ganciclovir are often used for treatment, it has been reported that acyclovir reduces viral shedding into the pharynx but does not improve symptoms [9, 10]. Ganciclovir has been reported to reduce EBV DNA load in patients with human immunodeficiency virus-related primary central nervous system lymphoma [11]. However, the efficacy of ganciclovir for EBV encephalitis has only been reported in a few cases of post-transplant patients [12]. As for immunotherapy, there are no double-blinded, randomized controlled clinical trials. The therapeutic strategy for EBV encephalitis remains to be identified. However, in a previously reported case of EBV encephalitis with vasculitis, symptoms and contrast enhancement suggestive of vasculitis improved after initiating acyclovir and steroids [4]. In the present case, both symptoms and punctate-enhanced lesions improved after intravenous methylprednisolone and IVIg. Immunotherapy may be effective in the treatment of EBV encephalitis with CLIPPERS-like lesions.
| Case                  | Age | Sex | Immunosuppression | Initial symptoms                                                                 | Gadolinium-enhanced MRI                  | Pathology                                                                 | Time from onset to treatment | Treatment                                           | Outcome                                                                 |
|----------------------|-----|-----|-------------------|-----------------------------------------------------------------------------------|------------------------------------------|---------------------------------------------------------------------------|------------------------------|-----------------------------------------------------|------------------------------------------------------------------------|
| Di Carlo et al. [4]  | 19  | Male| None              | Fever, consciousness disturbance (GCS 12), blurred vision, and diplopia           | Enhancement of cerebral vessels         | N/A                                                                       | 7 days                       | Acyclovir and methylprednisolone                     | No sequelae other than diplopia Enhancement of cerebral vessels disappeared |
| Kano et al. [7]      | 75  | Female| Rheumatoid arthritis treated with methotrexate and prednisolone | Fever and consciousness disturbance (GCS 13; E4V3M6)                              | Irregular ring enhancement in the right parietal lobe | Perivascular lymphocytic infiltration mainly consisting of CD3+ and CD8+ cells (biopsy) | A few days                   | Methylprednisolone and acyclovir                     | Bed-ridden with slight improvement of consciousness                  |
| The present case     | 82  | Male| None              | Fever and consciousness disturbance (GCS 10; E3V2M5)                              | Punctate enhancement in the bilateral basal ganglia                               | N/A                                                                       | 6 days                       | Acyclovir, methylprednisolone, and IVIg               | Discharge to nursing facility with improvement of consciousness Punctate enhancement disappeared |
Statement of Ethics

The authors declare that all work was conducted in accordance with the World Medical Association Declaration of Helsinki. Ethical approval was not required for this study in accordance with local guidelines. Written informed consent was obtained from the patient’s son, who was permitted to provide consent on behalf of the patient, for publication of the detail of his medical case and any accompanying images.

Conflict of Interest Statement

The authors declare that there is no conflict of interest.

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Author Contributions

Takafumi Wada wrote the first draft of the paper, which was reviewed by each co-author (Toru Yamamoto and Akihiko Ozaki). All authors contributed to the clinical care of the patient.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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