

# Acute Disseminated Encephalomyelitis Associated with Cytomegalovirus Infection in an Immunocompetent Subject

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**Abstract:** *Purpose:* Fulminant acute disseminated encephalomyelitis (ADEM) associated with cytomegalovirus (CMV) infection in immunocompetent hosts is rare, and the MRI findings might be atypical. *Case report:* A 17-year-old immunocompetent man presented with acute flaccid paraplegia accompanied by bladder and bowel incontinence. The serum virology tests revealed the presence of CMV IgM and IgG, indicating reactivation of latent infection. MRI studies of the brain and the whole spinal cord showed diffuse gray matter lesions of hyperintense signals in T2. After aggressive rescue therapy combining intravenous immunoglobulin, pulse methylprednisolone and plasma exchange, the patient made a complete neurological recovery 6 months later. *Conclusion:* This report demonstrates the association of CMV infection with ADEM in an immunocompetent subject. Although the treatment regimen and timing for patients with ADEM need further investigation, aggressive rescue therapy by adopting multiple immunomodulatory treatments may be warranted.

**Keywords:** ADEM, CMV, Immunocompetent, Gray matter.

## INTRODUCTION

Cytomegalovirus (CMV) shares the same ability to establish a long-lived latent infection as other members of the herpes virus family. The mainstays of the routes of transmission are vertical infection (in utero, while vaginal delivery, and via breast milk) and body fluids contact (saliva, genital, urine). Another two additional spreading routes are blood transfusion and organ transplantation. CMV is often acquired early in life, thus leading to a 15 to 20% seroprevalence by 15 years of age in the developed countries. Owing to more sexual exposure and crowded living, there is a steady upward trend of 1 to 2% per year from that age on [1]. In immunocompetent individuals, primary CMV infection rarely causes illness, which typically runs a benign, self-limited course. The reactivation of the latent virus caused the majority of symptoms while the hosts are in an immunocompromised status. Very few cases of ADEM associated with CMV infection in immunocompetent subjects have been reported in the medical literature [2].

Acute disseminated encephalomyelitis (ADEM) is an autoimmune monophasic demyelinating CNS disorder and predominantly affects the white matter of brain and spinal cord. Approximately 70 % of cases have antecedent viral infections [3]. A prodromal phase with flu-like symptom may be observed shortly before rapid onset of multifocal neurologic deficits, including pyramidal signs, sensory deficits, visual loss, ataxia, and spinal cord lesions. None of cerebrospinal fluid

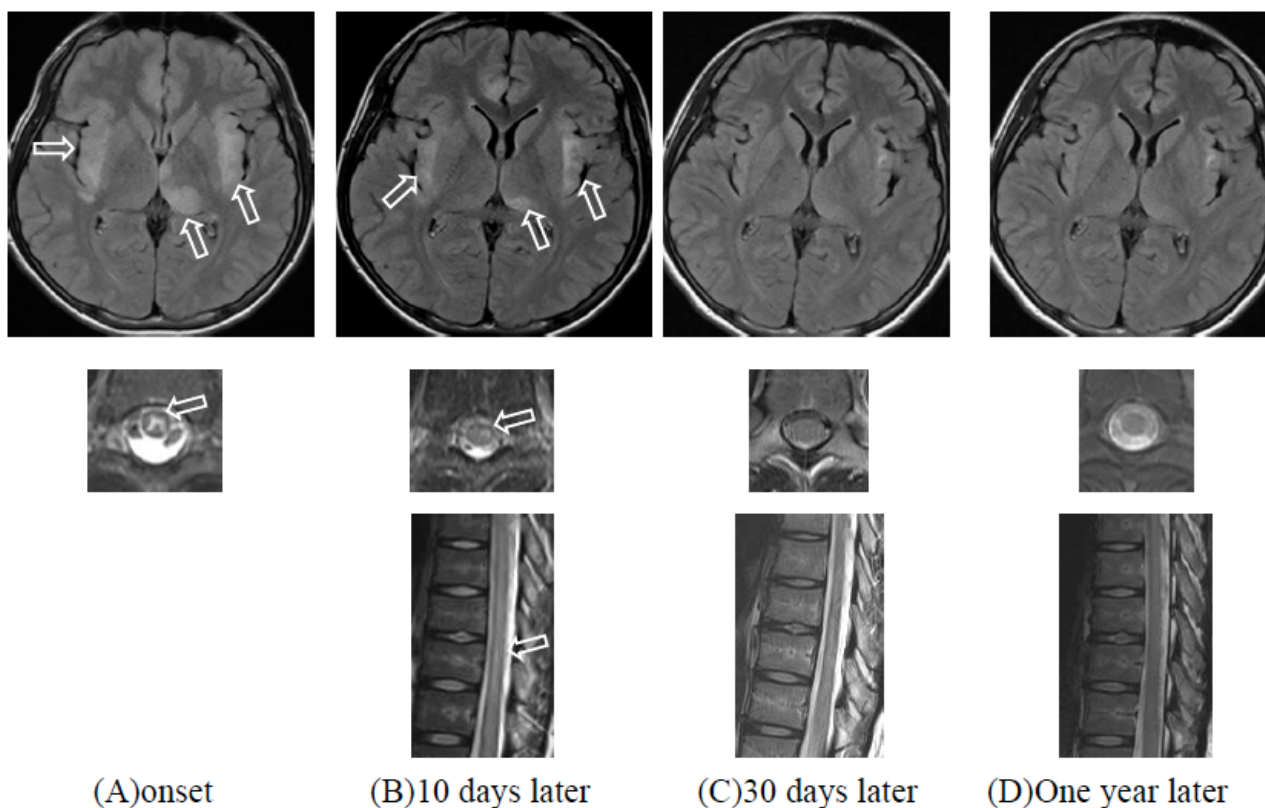
(CSF) findings and biologic markers is specific to ADEM. The most useful diagnostic investigation is magnetic resonance image (MRI), which commonly reveals multifocal brain and/or spinal cord lesions. To date, some forms of immunomodulatory therapies, including steroids, intravenous immunoglobulin (IVIg), or plasmapheresis, have been employed for ADEM, although there have been no randomized controlled trials to define the standardized therapy. Despite dramatic clinical and radiological presentations, two-thirds of patients make a full recovery, whereas 30% of patients have residual deficits and 5% die in the acute phase over one to six months [4].

We report a young man who had ADEM associated with CMV infection and atypical MRI findings.

## CASE REPORT

This 17-year-old male senior high school student had been healthy until one week before the admission, when he started to experience dizziness, mild sore throat, dysuria with a feeling of residual urine, and difficulty in walking. He went to a urologic clinic, and was diagnosed to have urinary tract infection (UTI) and urinary retention. Single catheterization was performed and oral antibiotics were prescribed. Two days prior to the hospitalization, dysuria exacerbated and he received another catheterization. On the morning of the admission day, he woke up feeling weak and numb in both legs and was unable to lift his legs. He was then sent to the emergency department. He did not report fever, headache, diplopia, dysphagia, respiratory distress, chest pain, abdominal pain, low back pain, body weight loss, or trauma.

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**Figure 1:** Series change of brain lesions on T2WI and T2 FLAIR images. **(A)** Multiple relative ill-defined hyperintense signal lesions involving the posterior part of pons, peri-aqueduct, Lt thalamus, bilateral insular cortex, bilateral frontal parasagittal cortex cingulate gyrus, Lt temporal base cortex, and whole spinal cord. These lesions mainly confined to gray matter. **(C)** After immunomodulatory therapy, signal intensity decreased in the area of the lesion as compared to that on the initial MRI. **(D)** These lesions almost disappear on a series of follow-up MRI images.

On examination, he was drowsy but could be roused to communicate. His heart rate was 94/min, respiratory rate 14/min, temperature 36.3°C, and blood pressure 155/85 mmHg. There was no nuchal rigidity, no abnormal breathing sound, no abdominal bruit, and no cold extremities. Neurologically, the muscle test revealed grade 5/5 proximally and grade 4/5 distally in the upper limbs, and 0/5 in thighs, legs, and feet. He was unable to roll or sit up. Areflexia in all four limbs and bilateral plantar extensor responses were detected. Neither atrophy nor fasciculation was present in the extremities. The patient had nearly complete loss of pinprick, thermal, vibration, and joint position senses below the T6 dermatome level. The anal sphincter sensation was absent, and urinary retention was noted. The remaining neurologic test results were unremarkable.

Routine laboratory workup yielded normal results. Hemogram showed normal white blood cell count (8300/uL) with relatively elevated monocyte proportion (10.7 %). Hemoglobin, platelets count, liver and renal function tests, C-reactive protein, and electrolytes were

normal. Electroencephalography showed generalized slow waves. Emergent MRI of head and spine revealed multiple ill-defined hyperintense lesions involving the posterior part of pons, peri-aqueduct, left thalamus, bilateral insular cortex, bilateral frontal parasagittal cortex, left temporal base cortex, and central gray matters over the whole spinal cord on T2-weighted and T2 fluid-attenuated inversion recovery (FLAIR) sequences (Figure 1A). All the brain lesions showed no enhancement, but the lesions at the gray matter of spinal cord showed fluffy enhancement.

CSF studies demonstrated an opening pressure of 80 mm CSF and cytoalbuminologic dissociation with cell count of 0 and total protein of 560 mg/dL. CSF culture and extensive microbiologic workup showed no sign of bacteria, virus, cryptococcus, fungus, and syphilis. Tests on cytology, oligoclonal bands, and IgG index of CSF reported no abnormal results. Serum anti-aquaporin 4 (AQP4) antibodies were negative and visual evoked potentials revealed normal responses. Consequently, we find a strong association between ADEM and CMV.

Extensive diagnostic assessment to identify antecedent infection, including antibodies to polio, varicella zoster, rubella, and herpes simplex viruses, revealed negative results. Epstein-Barr virus was determined as a remote infection. Serum virology study reported reactivation of latent CMV infection based on the presence of CMV IgM of 2.7 AU/mL and CMV IgG of 76.4 AU/mL. Polymerase chain reaction (PCR) testing for CMV on a CSF sample was negative. The results from additional tests, including autoimmune antibodies, tumor markers, and anti-human immunodeficiency virus antibody, indicated that he was not immunocompromised.

Considering the concomitant UTI, we administered IVIg with a dosage of 0.4mg/kg/d for five consecutive days instead of steroid. The clinical encephalopathic symptom of drowsiness improved. After watchful observation for two weeks, the patient did not regain any muscle power even though follow-up MRI showed diminished gray matter lesions (Figure 1B).

After UTI was completely treated, we tried pulse therapy with intravenous methylprednisolone (MTP) 1000 mg daily for 2 days. There was no significant improvement in the neurological deficits. Thus, we initiated another combination protocol [5-7], which included simultaneous pulse MTP for 5 days and 5 courses of plasma exchange (approximately 2.5 L of plasma with mean flow rate of 20 ml/min in each session of plasmapheresis). He responded well to this combination treatment, and the muscle strength of his feet started to improve after the 3rd PE, and he made steady progress in the resolution of the neurological symptoms under regular rehabilitation. On the follow-up MRI in one month, the original abnormal signals had decreased markedly as compared to those on the initial MRI (Figure 1C). Urinary bladder function recovered two months after onset. In six months, he regained full muscle strength in the lower extremities and was able to walk and run without difficulties. Follow-up MRI in one year showed no abnormal enhanced lesions in bilateral cerebral hemispheres, and myelomalacia at T3-T8 levels with hyperintense T2 signals, which were consistent with previous CMV-induced ADEM (Figure 1D).

## DISCUSSION

This case report illustrates the following important clinical issues for ADEM: (a) atypical MRI findings, (b)

antecedent CMV infection in immunocompetent hosts, and (c) the efficacy of immunosuppressive therapy.

The patient presented with acute neurological dysfunction as mild lethargy and severe myelopathy, and the MRI studies revealed multifocal CNS inflammatory lesions. He had remarkable improvement clinically as well as in serial imaging studies. The encephalopathic presentation in our patient was mild and lasted for a short period. According to a case series of ADEM, encephalopathic symptoms vary widely in severity and over half of the patients may have only mild alteration of consciousness, such as sleepiness and/or irritability [8]. Therefore, we believe that the diagnosis of this case was consistent with the 2007 Consensus of the National Multiple Sclerosis Society, in which ADEM is defined as a monophasic demyelinating multifocal CNS disorder either in clinical presentations or in neuroimage studies [9].

Notably, the MRI studies showed lesions involving deep and cortical gray matter in the brain and central gray matter over the whole spinal cord. Although large multifocal asymmetric white matter lesions are characteristic of ADEM, previous studies have reported that involvement of cortical gray matter and deep gray matter structures, including the basal ganglion and thalamus, is common and the gray matter of ADEM is often in a symmetric fashion [10]. These findings highlighted that ADEM is not completely a disease of white matter. Furthermore, Monden *et al.* reported a young patient with ADEM with atypical spinal MRI findings of a centrally-located long spinal cord lesion (LCL), which was defined as contiguous spinal cord abnormalities extending more than three vertebral segments [11]. The MRI manifestation of LCL has been reported as a characteristic finding in cases of neuromyelitis optica (NMO) [12]. The other differential diagnoses of LCL include infections, tumors, vascular diseases, and autoimmune diseases. In our subject, NMO could be excluded because the serum anti-AQP4 antibody was negative and there was no clinical evidence of optic neuritis. The extensive workup tests for etiology had excluded other possibilities. Although not typical, the MRI manifestations in our patient still could be seen in ADEM.

Virtually all CMV infections occurring in immunocompetent people are asymptomatic or self-limited. Some patients manifested a mononucleosis-like syndrome. The most frequent presentation is prolonged

duration (around 7.8 weeks) of malaise, jaundice, night sweats, fever, hepatitis and lymphadenopathy [13]. This raises an intriguing question of why our patient, a fully immunocompetent male, developed fulminant ADEM. When the immune mechanisms, especially those mediated by CD4<sup>+</sup> and CD8<sup>+</sup> lymphocytes, fail, latent CMV virus can reactivate and cause direct and indirect injury. Necrotizing CMV retinitis and esophagitis are typical examples of direct virally mediated diseases. CMV pneumonitis, myocarditis, enteritis, vasculitis, hepatitis and meningoencephalitis are examples of indirect immune-mediated injury, which may result from the upregulation and release of cytokines (1). Moreover, another potential mechanism for CMV-induced ADEM is based on the structural similarity between human CMV major capsid protein and encephalitogenic myelin/oligodendrocyte glycoprotein (MOG 34–56) [14]. In short, reactivation from the latent state and immune-mediated injury result in ADEM.

To date, there have been no randomized controlled trials to define the most efficacious immunomodulatory therapy for ADEM. Steroid treatment remains to be the most widely employed for patients with ADEM. Previous studies reported 50 to 80% of patients obtained full recovery after aggressive high-dose IV MTP (10 to 30 mg/kg/day up to maximum dose of 1g/day) for 3 to 5 day followed by 4 to 6 weeks of oral steroid tapering regimens [4]. In the consensus, IVIg is a reasonable option, either alone or in combination, as a second-line therapy for ADEM in patients who do not respond to high-dose corticosteroids or who have contraindications for first-line steroid therapy. In general, a total dose of 2 g/kg given over 2 to 5 days for adults and 2 days for children is reasonable [15]. The role of plasma exchange in ADEM is a rescue therapy when other modalities fail. Some case reports documented that plasma exchange might be more effective while it was given early in the disease course [5-7]. After the initial failures for single therapy of steroid and IVIg, our case tolerated and responded well to the combined multimodal immunomodulatory therapies. With the clinical recovery, the follow-up MRI studies showed complete resolution in the brain but cavitation in the thoracic spinal cord.

## CONCLUSION

In this case, ADEM is considered to be associated with a preceding CMV infection, and presents with atypical CNS lesions involving extensive gray matters

in MRI studies. Aggressive rescue therapy with combination regimens is worth trying in view of the favorable response.

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