Acute disseminated encephalomyelitis in an elderly patient following pneumococcal vaccination with extremely high cerebrospinal fluid interleukin-6

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Abstract

Background: Postvaccination acute disseminated encephalomyelitis (ADEM) may develop 2–30 days after various vaccinations, such as rabies, diphtheria-tetanus-polio, smallpox, measles, mumps, rubella, Japanese B encephalitis, pertussis, influenza, and hepatitis B. Pneumococcal vaccination is recommended for elderly patients and has been publicly funded in Japan since 2014. Here we report an extremely rare case of an elderly patient who developed ADEM following 23-valent pneumococcal polysaccharide vaccine (PPSV23) administration.

Case presentation: We report a 73-year-old woman with ADEM following pneumococcal vaccination. She developed acute fever and consciousness disturbance 17 days after the second administration of 23-valent pneumococcal polysaccharide vaccine (PPSV23). Head magnetic resonance imaging (MRI) revealed numerous T2-high lesions, mainly involving the cerebral and cerebellar white matter and brainstem. Cerebrospinal fluid examination showed polymorphonuclear pleocytosis and markedly elevated interleukin-6 (58,400 pg/ml). Her symptoms and MRI lesions were promptly resolved by steroid pulse therapy, with no relapse.

Conclusion: Although PPSV23 is recommended for elderly individuals, this case highlights the risk of ADEM caused by unexpected immune activation following repeated administration of the vaccine.

Keywords
acute disseminated encephalomyelitis, interleukin-6, pneumococcal vaccine, postvaccination
Blood tests showed increased white blood cells (10,260/μl; neutrophils 80%, lymphocytes 15.9%), and elevated C-reactive protein (2.88 mg/dl), D-dimer (1.8 μg/ml), and interleukin (IL)-6 (71.2 pg/μl). Other blood counts, biochemistry, and coagulation, including PT (11.9 s) and APTT (29.7 s), were normal. Autoantibodies, including anti-aquaporin 4 (AQP4), anti-glutamic acid decarboxylase, anti-myelin oligodendrocyte glycoprotein (MOG), anti-nuclear, anti-SS-A/B, and anti-neutrophil cytoplasmic antibodies were all negative. Tumor markers were negative, and soluble IL-2 receptor (sIL-2R) levels were normal (199 U/ml). T-SPOT was negative, and blood cultures produced no bacterial growth. Cerebrospinal fluid (CSF) analysis demonstrated normal opening pressure (70 mmH₂O), xanthochromic appearance, increased cell counts (480/μl; mononuclear cells 14%, polymorphonuclear cells 86%), and protein levels (327.1 mg/dl), normal glucose levels (71 mg/dl, simultaneous blood glucose 146 mg/dl), elevated myelin basic protein (MBP) (1610 pg/ml), and increased IgG index (0.904) without oligoclonal bands. CSF IL-6 (58,400 pg/ml) and sIL-2R levels (199 U/ml) were increased. Herpes simplex virus DNA was negative by polymerase chain reaction. Angiotensin-converting enzyme (0.6 U/L) and adenosine deaminase (3.2 U/L) levels were

**FIGURE 1** Brain MRI on day 3 from onset and follow-up. (a) FLAIR images showing numerous high-signal intensity lesions mainly involving the cerebral white matter. The cerebellar white matter, brainstem, left thalamus, and bilateral basal ganglia were also affected. (b) T2-weighted image showing high-signal intensity lesions similar to FLAIR images. (c) T1-weighted image showing minimally low-signal intensity lesions in the left thalamus. (d) DWI showed no signal changes. (e) ADC map showing elevated ADC value lesions with a similar distribution to FLAIR and T2-weighted images. (f) Gadolinium-enhanced T1-weighted images showed no enhancement. The same axial plane surrounded by a square in (a) is shown in (b–f). (g) FLAIR images taken on Days 3, 6, 16, 24, and 32 from onset (left to right) showing successive resolution of high-signal intensity lesions after treatment with steroids. (h) DWI images on Days 6, 10, and 16 from onset (left to right) showing high-signal intensity lesions in the right centrum semiovale, pons, and right cerebellar hemisphere, respectively.
normal. CSF cytology was unremarkable. Blood and CSF cultures were negative for bacteria and *Mycobacterium tuberculosis*. No neoplastic lesions were detected by cervical to pelvic computed tomography. Electroencephalography demonstrated prominent diffuse slow waves, but no epileptic discharges. Nerve conduction was normal.

Head magnetic resonance imaging (MRI) on Day 3 revealed numerous fluid-attenuated inversion recovery (FLAIR)- and T2-high-signal intensity lesions, mainly involving the cerebral white matter, and the cerebellum, brainstem, left thalamus, and bilateral basal ganglia were also affected (Figure 1A). These lesions displayed low-to-intermediate signal intensities on T1, intermediate intensities on diffusion-weighted imaging (DWI), and increased apparent diffusion coefficient (ADC), suggesting vasogenic edema (Figure 1B–E). Gadolinium enhancement was not evident in any lesion (Figure 1F). Whole spinal cord MRI was normal.

Steroid pulse therapy (methylprednisolone 1000 mg/day for 3 days) was initiated on the admission day, repeated twice, followed by oral prednisolone (50 mg/day) with gradual tapering (Figure 2). Meropenem (2000 mg every 8 h) and vancomycin (750 mg every 12 h) were adjunctively administered until her blood and CSF cultures were negative. Her fever and consciousness disturbance promptly resolved. CSF on Day 17 showed decreased cell counts (10/μl, mononuclear cells 100%) and protein (73.4 mg/dl), MBP (56.1 pg/ml), and IL-6 (8 pg/ml) levels. Follow-up head MRI on Days 3, 6, 16, 24, and 32 demonstrated successive resolution of FLAIR-high-signal intensity lesions (Figure 1G). No new neurological abnormalities developed, but DWI on Days 6, 10, and 25 disclosed asymptomatic punctate acute cerebral infarctions in the right cerebral hemisphere, left pons, and right cerebellar hemisphere, respectively (Figure 1H). The patient was followed up until 5 mo after onset, with no relapse or new MRI lesions.

2 | DISCUSSION

A first acute clinical event of encephalopathy with multiple FLAIR- and T2-high lesions involving the cerebral and cerebellar white matter and brainstem, without subsequent clinical relapse or new MRI lesions, indicated a diagnosis of ADEM in this case, based on the International Pediatric MS Study Group criteria. Although the patient had thalamic and basal ganglia lesions, deep gray matter involvement may also occur in this condition. Increased CSF MBP suggested demyelination, while an absence of anti-MOG and anti-AQP4 antibodies, together with the lack of longitudinally extensive spinal cord lesions and optic neuritis, excluded neuromyelitis optica spectrum disorders (NMOSD) and MOG-associated disease. We therefore diagnosed the patient with ADEM associated with pneumococcal vaccination.

ADEM has an overwhelmingly pediatric predilection, partly attributable to frequent vaccination in children. PPSV23 vaccination covering 23 pneumococcal subtypes is recommended for elderly individuals at risk of devastating pneumococcal infections. Although PPSV23 vaccination is generally thought to be safe, the second vaccination may cause stronger immune/inflammatory reactions than the first. Indeed, in a study of two pharmacovigilance databases, postpneumococcal vaccine ADEM accounted for about 3% of vaccine-associated ADEM events, although these databases lacked detailed case descriptions and rigorous case verification, and included cases with possible (33%), unlikely (14%), and unrelated (15%) causality. A case of NMOSD relapse following PPSV23 in an elderly patient was also reported, suggesting that complement activation induced by pneumococcal vaccination may in part be contributory to the relapse.

In our patient, CSF IL-6 levels were markedly elevated. IL-6 is a pleiotropic cytokine inducing a proinflammatory response. It was reported that IL-6 in CSF was significantly increased in adult patients with ADEM compared with patients with other neurological diseases, and showed a significant positive correlation with CSF cell counts. IL-6 is also markedly elevated in the CSF in patients with NMOSD presenting with frequent polymorphonuclear pleocytosis. Anti-IL-6 receptor monoclonal antibody has beneficial effects in NMOSD. Together, these observations suggest a critical role of IL-6 in inducing neuroinflammation. The highly elevated IL-6 levels in our patient may have contributed to CSF polymorphonuclear pleocytosis. Alternatively, molecular mimicry between pneumococcal antigens and myelin proteins may cause PPSV23-associated ADEM, as suggested by a case report of ADEM-like meningoencephalitis following post-pneumococcal pneumonia. Concomitant minor stroke-like lesions in our patient could be cardiogenic or artery-to-artery embolism, as indicated by the increase in D-dimers with normal PT and APTT.

In conclusion, clinicians should be aware that, although a second vaccination of PPSV23 is warranted to prevent pneumococcal
infection in elderly individuals, it is associated with a risk of postvaccination ADEM resulting from a strong inflammatory reaction.

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CONFLICT OF INTEREST
Y.K., T.T., and N.M. have nothing to declare.

DATA AVAILABILITY STATEMENT
Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

DISCLOSURE OF ETHICAL STATEMENTS
Approval of the research protocol: N/A.
Informed consent: All informed consent was obtained from the subject(s) and/or guardian(s).
Registry and the registration no. of the study/trial: N/A.
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