4세 남아에서 발생한 *Mycoplasma pneumoniae* 감염이 동반된 중증 뇌염 1예

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A Case of Severe Encephalitis with *Mycoplasma pneumoniae* Infection in a 4-Year-Old Boy

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Mycoplasma pneumoniae (MP) infection can result in extrapulmonary and respiratory manifestations. The direct invasion by MP and the indirect invasion by immune-mediated response have been suggested as the pathogenesis of extrapulmonary manifestations. Neurologic manifestations are the most common among the extrapulmonary manifestations associated with MP infection. We report the case of a 4-year-old previously healthy boy with encephalitis accompanied by MP pneumonia. The patient's respiratory manifestations appeared 14 days before the neurological manifestations. Leukocytosis was observed in the patient's cerebrospinal fluid, but the result of the MP polymerase chain reaction was negative. The magnetic resonance imaging of the patient's brain showed high signal intensity at bilateral basal ganglia. The chest radiograph confirmed the presence of lobar pneumonia. The serological test on MP-specific immunoglobulin M titer revealed a positive result. The clinical course improved with the administration of immunomodulatory therapies, but the patient subsequently developed spastic quadriplegic cerebral palsy. MP is a common pathogen in children and may induce aggravating neurologic diseases. Thus, MP should be considered a causative agent of encephalitis in children. Immunomodulatory drugs are the recommended therapeutic option for severe MP encephalitis.

Key Words: *Mycoplasma pneumoniae*, Encephalitis

Introduction

Mycoplasma pneumoniae (MP) is a common pathogen that causes community-acquired pneumonia in children and young adults. MP infection presents as various clinical manifestations, from a respiratory tract infection to severe extrapulmonary diseases. The extrapulmonary symptoms can have a wide spectrum and may manifest as cardiovascular, dermatological, hematological, musculoskeletal, urogenital, neurological, and digestive organ symptoms¹⁾. Neurologic manifestations, such as encephalitis, aseptic meningitis, Guillain-Barré syndrome, acute transverse myelitis, stroke, and polyradiculopathy, are the relatively common extrapulmonary manifestations of MP infection. These diverse neurologic manifestations can occur even without an accompanying respiratory

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manifestation²⁻⁴). Herein, we report a case of encephalitis associated with MP infection in a previously healthy boy who underwent severe clinical course and recovered with immunomodulatory treatments.

Case report

A 4-year-old previously healthy boy was referred to the

emergency room with chief complaints of repetitive generalized tonic-clonic seizures. He had no history of other diseases or seizures. There was no family history of epilepsy or febrile seizure. Two weeks ago, he was hospitalized for pneumonia at a local clinic, and his condition improved. However, fever with productive cough and rhinorrhea recurred abruptly. His mother and father were admitted to our hospital for lobar pneumonia the next day.

On hospital day 1, with increasing body temperature (38.4°C), he presented with altered consciousness and partial tonic-clonic seizures of right hand and foot. During the seizure, both eyeballs deviated upward for about 5 min; this resolved with lorazepam injection and intravenous administration of fosphenytoin loading doses. On chest X-ray, increased pneumonic infiltration in the right middle and lower lobes was observed (Fig. 1). Laboratory findings revealed leukocytosis (29,280/ μ L; neutrophil, 91.7%), elevated C-reactive protein (13.73 mg/dL, reference range: 0–0.5 mg/dL), and elevated procalcitonin (1.704 ng/mL, reference range: 0–0.5 ng/mL). Prothrombin time was 17.0 sec (international normalized ratio, 1.36); activated partial thromboplastin time was 50.5 seconds; fibrin/fibrinogen degradation products were 8.40 μ L/mL; D-dimer was 1.34 μ L/mL; fibrinogen was 476 mg/dL; antithrombin III was 80%; and the platelet count was 212,000/ μ L. Serum MP immunoglobulin M (IgM) was positive at the index of 4.6 (positive value: > 1.1 index) and increased to a peak index of 7.8 during hospitalization. No bacterial growth was observed in any blood, urine, and sputum specimens. A lumbar puncture showed the following values for the cerebrospinal fluid (CSF): leukocytes, 650 cells/ μ L; red blood cells, 90 cells/ μ L; glucose, 64 mg/dL; and protein, 79.8 mg/dL.

Fig. 1. Initial chest X-ray shows the increased pneumonic infiltration in right middle and lower lobes.

Fig. 2. Magnetic resonance imaging on 2nd hospital day. (A) Diffusion-weighted imaging shows bilateral symmetric high signal intensity at both basal ganglia (wide white arrows). (B) Apparent diffusion coefficient sequence shows no diffusion restriction. (C) Apparent bilateral symmetric increased signal intensity at both basal ganglia on fluid-attenuated inversion-recovery image (wide white arrows). (D) There is no obvious change yet on T2-weighted image.

There was no bacterial growth on CSF culture. CSF polymerase chain reaction (PCR) tests were negative for MP, enterovirus, and herpes simplex virus types 1 and 2. We diagnosed him as having meningoencephalitis and disseminated intravascular coagulation with lobar pneumonia. Parenteral therapy with immunoglobulin (500 mg/kg for 4 days), vancomycin, cefotaxime, acyclovir, clarithromycin, and fosphenytoin were administered. On hospital day 2, he presented with tonic-clonic seizure on the right side and subsequent hypomotor seizure for about 15 min. Brief seizure attacks repeatedly recurred, and the patient was transferred to the intensive care unit. Magnetic resonance imaging (MRI) of the brain showed high signal intensity at both basal ganglia on diffusion-weighted imaging (DWI) and fluid-attenuated inversion-recovery (FLAIR) images (Fig. 2). Continuous electroencephalography (EEG) showed diffuse cerebral dysfunction and nonconvulsive status epilepticus (Fig. 3). He received ventilator care and continuous infusion of midazolam to control the seizures. Parenteral methylprednisolone pulse treatment (30 mg/kg/day for 3 days) was administered, and fosphenytoin, phenobarbital, levetiracetam, and valproic acid were added as antiepileptic drugs. On hospital day 14, brain MRI showed bilaterally symmetric increased signal intensity at both basal ganglia and both cerebral cortex with diffuse gyral swelling on DWI and T2-weighted image (T2WI) (Fig. 4). The last seizure with right hemiconic movement was observed on hospital day 23. On hospital day 54, he was discharged in a bedridden state after receiving the inpatient rehabilitation schedule for spastic quadriplegic cerebral palsy and was prescribed oral levetiracetam for postencephalitic epilepsy. At the time of discharge, brain MRI showed distinct symmetric high signal intensity and atrophic changes at both hemispheres on FLAIR and T2WI (Fig. 4).

Discussion

The pathomechanisms of extrapulmonary diseases associated with MP infection remain uncertain^{1). Narita¹⁾ classified them into the following three types: a direct type, in which the organism exists at the lesion and induces local inflammatory cytokines; an indirect type, in which the organism does not exist at the lesion but induces immune modulations; and a vascular occlusion type,}

Fig. 4. Magnetic resonance imaging (MRI) on 14th hospital day shows bilateral symmetric increased signal intensity at both basal ganglia (arrowheads) and both cerebral cortex with diffuse gyral swelling on diffusion-weighted imaging (A) and T2-weighted image (T2WI) (B). On 54th hospital day, follow-up MRI shows distinct symmetric high signal intensity and atrophic changes at both hemispheres on fluid-attenuated inversion-recovery (C) and T2WI (D).

Fig. 3. An electroencephalography shows diffuse suppressed background activities and several repetitive episodes of generalized high-voltage spike and wave discharges.

in which the organism induces vasculitis or thrombosis, MP can lead to the formation of immune complexes and release of cytokines and chemokines, which play essential roles in the development of both pneumonia and extrapulmonary manifestations³. The pathogenesis of immune-mediated injury is not certain; however, it is likely that antigenic similarities between MP and human organs are an important factor. The immune complexes formed by MP infection deposit in small venules of the central nervous system (CNS), and are responsible for diverse neurologic manifestations⁵.

MP infection is responsible for 5%–10% of cases of acute encephalitis in children⁶. MP encephalitis can be classified into two distinct patterns, according to the time of onset of neurologic manifestations. In early-onset encephalitis, these appear within 7 days of fever onset. In late-onset encephalitis, they do not appear until the 8th day or later³. A study by Al-Zaidy et al.⁴ supported the validity of these two patterns. A prolonged prodrome (≥ 7 days) was associated with respiratory symptoms, peripheral blood IgM, and presence of MP in the respiratory tract, but absence of MP in the CSF. Conversely, a brief (< 7 days) or absent prodrome was less frequently associated with respiratory symptoms and IgM response. In these cases, MP was detected in CSF but not in the respiratory tract.

The incidence of positive PCR results for MP in CSF is reportedly variable but typically low. In data from the Swiss national surveillance system⁷, MP was not detected in the CSF of any patient, but was detected in throat specimens from 85% of patients. All patients experienced a respiratory prodromal period of at least 5 days before neurologic manifestation, and 83% were confirmed to have pneumonia on chest radiography. Hu et al.⁸ reported that all CSF specimens were negative for MP on PCR. A study by Christie et al.⁹ and another study⁵ reported that only 2% and 12% of CSF specimens were positive for MP on PCR, respectively.

In our case, the facts that radiological findings for pneumonia, respiratory symptoms, and peripheral blood IgM were present, and that neurologic manifestations appeared 8 days later, suggest the possibility of late-onset encephalitis induced by an immune-mediated mechanism.

Taking into account the immune-related response, the absence of MP in the CSF does not eliminate the possibility of an MP infection. Identifying the presence of MP in the respiratory tract may play an important role in confirming MP as the responsible organism in acute encephalitis. MP infection can be demonstrated by PCR, culture of the CSF and throat, seroconversion of serum antibody titer, or the presence of MP-specific IgM⁵. Although neither PCR nor culturing of throat swab samples

for MP were performed in our case, positive results were obtained for MP-specific antibodies.

To date, although various treatments have been proposed for the treatment of MP infection-associated CNS diseases, no consensus has yet been established. Macrolides are the first-line antibiotics to treat pneumonia with MP infection in children¹⁰. Because of their high molecular mass and low affinity, however, they are incapable of passing through the blood–brain barrier and reaching therapeutic concentrations in the CNS¹¹.

From an immunopathogenic perspective, immunomodulatory therapy may be an effective strategy for MP encephalitis. Corticosteroids may be useful in the treatment of severely ill MP encephalitis patients¹². Intravenous immunoglobulin (IVIG) can reportedly improve the state of patients with acute disseminated encephalomyelitis, or encephalitis affecting the brainstem and striatum^{13,14}. In our case, the clinical course did not improve rapidly despite the use of IVIG and high-dose methylprednisolone. However, these treatments may have shortened the duration of recovery.

Compared with other bacterial or viral encephalitis patients, MP encephalitis patients show a lower frequency of seizures and a better clinical course⁹. Neurologic sequelae, however, are common in MP encephalitis, occurring in 43%–64% of cases^{5,7}. Hu et al.⁸ suggested that high IgM titers, and a long interval between respiratory illness and onset of neurologic symptoms, may predict worse outcomes in patients with MP encephalopathy. In our case, the MP IgM titer (index 7.8) was relatively high compared to the cutoff value (index > 1.1), and the prodromal period was long (14 days). These two factors may have affected the prognosis of the patient.

In conclusion, encephalitis is a disease that can take a serious clinical course. Pneumonia may indicate the possibility of a remote onset of encephalitis provoked by MP infection. Clinicians should be aware that MP is a causative organism of encephalitis in children, even if the patient does not present any respiratory manifestation. Further studies are necessary to establish diagnostic tools and treatments for patients with MP encephalitis.

요약

Mycoplasma pneumoniae (MP) 감염은 호흡기 증상과 폐 외 증상을 일으킬 수 있다. 그 병태생리에 대해서는 아직 확립된 바가 없으나, MP의 직접 침범과 면역매개 반응에 의한 간접 침범이 주 기전으로 제시되고 있다. 폐 외 증상 중 신경계 합병증은 가장 흔하게 발생하는 증상이다. 우리는 이전에 건강하였던 4세 남아에서 발생한 MP

폐렴이 동반된 뇌염을 경험하였기에 보고하는 바이다. 환자는 신경학적 증상을 나타내기 14일 전에 호흡기 증상을 보였다. 뇌척수액 검사 상에서 백혈구 증가 소견을 보였으나, MP 중합효소 연쇄반응은 음성이었다. 뇌 자기공명영상 상에서는 양측 기저핵의 고 신호강도 소견을 보였다. 단순 흉부 방사선 검사 상 대엽성 폐렴이 확인되었고, 혈장 MP-특이 면역글로불린 M 결과는 양성으로 확인되었다. 환자의 임상 경과와 면역 조절 치료를 하면서 호전되었으나, 환아는 강직성 사지 뇌성마비 상태가 되었다. MP는 소아에서 흔한 병원체이며 심각한 신경학적 질병들을 유발할 수 있으므로 MP를 소아 뇌염의 원인 균주로 인식하려는 노력이 필요하다. 심각한 MP 뇌염에서는 면역 조절 약제를 치료적 선택의 하나로 고려해야 하겠다.

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