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Case Report

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A rare case of mild encephalitis/encephalopathy with reversible splenial lesion associated with *Mycoplasma pneumoniae* in an adult male

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Abstract

Mild encephalitis/encephalopathy with a reversible splenial lesion (MERS) is a clinically mild, radiologically reversible clinical condition. MERS associated with *Mycoplasma pneumoniae* is rare, and the diagnosis can be challenging. In this case report, an 18-year-old male patient with a history of travel from Saudi Arabia presented with a high fever, cough, headache, joint pain, nausea, and vomiting. He was referred to the emergency department with an increased tendency to sleep and a preliminary diagnosis of encephalitis. On physical examination, he was afebrile, hypotensive and bradycardic. Macular rashes on the chest and nystagmus in the right eye were observed. Meningeal irritation findings and Babinski signs were negative. Polymerase chain reaction (PCR) of the patient's nasopharyngeal swab specimen revealed *Mycoplasma pneumoniae*. Cerebrospinal fluid (CSF) analysis showed pleocytosis with polymorphonuclear leukocyte (PMN) dominance and elevated total protein. *M. pneumoniae* was undetected in CSF via PCR. Cranial magnetic resonance imaging revealed a well-defined, oval-shaped lesion at the midline level of the splenium of the corpus callosum. The patient was administered intravenous ceftriaxone, moxifloxacin, and a single dose of hydroxycobalamin. On day 2 of treatment, symptoms improved significantly and the patient was successfully discharged on day 7 upon clinical recovery. This report highlights that molecular tests are invaluable for the detection of rare pathogens in MERS cases.

Keywords: *Mycoplasma pneumoniae*, MERS, molecular detection, corpus callosum, neuroimaging

1. Introduction

Mild encephalopathy with a reversible splenial lesion (MERS) is a clinically mild, radiologically reversible clinical condition characterized by diffusion restriction in the splenium of the corpus callosum. Typically, it presents with central nervous system (CNS) disorders such as mental mood changes, delirium, seizures, muscle weakness, ophthalmoplegia, and headache, and has a favorable prognosis with complete recovery within a month (1). Depending on the neuroimaging findings, MERS is classified into type I, involving solitary hyperintensity lesions in the splenium of the corpus callosum, and type II, involving hyperintensity lesions in the corpus callosum and other brain areas (2). MERS is observed in both adults and children, with common etiological pathogens being influenza A and B viruses, rotavirus, measles virus, adenovirus, *Streptococcus pneumoniae,* and *Escherichia coli* (3). *Mycoplasma pneumoniae* infection-related MERS is rare, and only a few cases have been reported in the literature.

Mycoplasma pneumoniae is a major human pathogen which causes community-acquired pneumonia. The bacterium is mostly transmitted from person to person via respiratory droplets discharged by infected individuals. It can also be transmitted directly by touching an infected person's nasal or throat discharges, or indirectly through contact with goods that have been newly contaminated by secretions. The incubation period lasts from two to three weeks (4). *M. pneumoniae* infection is linked with a variety of CNS symptoms such as aseptic meningitis, encephalitis, acute transverse myelitis, and stroke, particularly in children. *M. pneumoniae* infections in the respiratory tract can spread to the CNS via gaps between epithelial respiratory cells, causing direct functional and structural abnormalities in several body systems, including the CNS. Mycoplasma encephalitis is an uncommon infectious encephalitis that causes neurological symptoms, including headache, altered consciousness, meningeal signs, convulsions, and behavioral disturbances. CNS symptoms can affect up to 7% of individuals hospitalized with the pathogen. About 53% of the patients with neurological symptoms caused by *M. pneumoniae* have been reported to be aged between 6 to 20 years of age, while only a few occurrences have been documented in people beyond middle age (5).

Diagnosis of *M. pneumoniae* infection is typically performed using either a polymerase chain reaction (PCR) assay or serological testing. *M. pneumoniae* encephalitis cannot be reliably detected in adults for the reasons that the rate of incidence is low, there are no radiologic or clinical signs and symptoms indicating a mycoplasma etiology of patients who

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have neurological symptoms, and there is no obvious diagnostic marker in the CSF. Therefore, PCR in throat swab specimens and/or serum antibodies are advised (5).

This report describes a case of an 18-year-old male patient presenting with MERS associated with *M. pneumoniae* diagnosed via molecular testing and magnetic resonance imaging (MRI).

2. Case Report

A previously healthy 18-year-old male was referred to our hospital emergency department. The patient had a travel history to Saudi Arabia 3 days earlier and presented with headache, fever, joint pain, cough, nausea, and vomiting. He was initially admitted to the Respiratory Diseases Department at a state hospital, where he was diagnosed with pneumonia and treated with ceftriaxone 2 x 1 g intravenously as an inpatient. During the treatment, the patient had an increased tendency to sleep and had no improvement in clinical symptoms. Due to clinical deterioration, he was transferred to the Neurology Department of a private hospital with a preliminary diagnosis of encephalitis, from where he was transferred to the Infectious Disease (ID) Department. On physical examination, the patient did not have a fever, but he was hypotensive and bradycardic. He had a loss of consciousness, a high tendency to sleep, nystagmus in his right eye, and a macular rash around his chest. The patient did not have any symptoms of meningeal irritation. Upon admission of the patient to the ID Department, a throat culture was performed, and it was reported to be negative for pathogenic bacteria. Salmonella tube agglutination (Grubel-Widal) test, Weil-felix (Proteus) test, and plasmodium rapid antigen test were also performed, and test results were negative. Patient's blood tests, including 30-minute and 60-minute sedimentation rate (5 and 9 mm/hour, normal range: 0-15 mm/hour), procalcitonin (0.05 ng/mL, normal range: 0.00-0.05 ng/mL), urea (21 mg/dL, normal range: 18-45 mg/dL), creatinine (0.84 mg/dL, normal range: 0.69-1.10 mg/dL), total bilirubin (0.95 mg/dL, normal range: 0.00-1.20 mg/dL), gamma-glutamyl transferase (20 U/L normal range: 12-64 U/L), alanine transaminase (ALT) (22 U/L, normal range: 0-55 u/l) and aspartate aminotransferase (AST) (31 U/L, normal range: 5-34 U/L) results were normal. The patient's blood creatine kinase levels were (418 U/L, normal range: 30-200 U/L) and blood C-reactive protein (CRP) levels were elevated (5.41 mg/dL, normal range: 0.00-0.50), while sodium levels were low (134 mmol/L, normal range:136-145). Laboratory investigations revealed a WBC count of 7600/µl (normal range: 4100-10900/µl). A sputum sample was obtained and was investigated for *Mycobacterium tuberculosis* complex using polymerase chain reaction (PCR) which was negative. An oro-nasopharyngeal sample and CSF samples were tested using the Qiastat-Dx Respiratory Panel and were positive for *Mycoplasma pneumoniae* (Fig. 1).

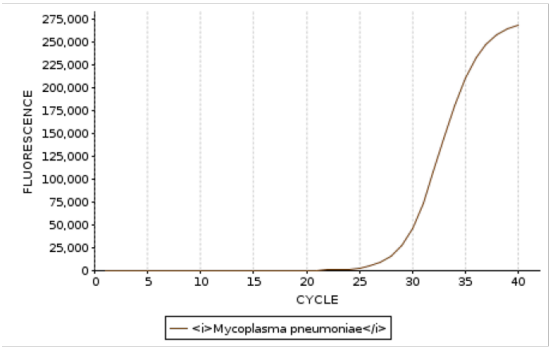

Fig. 1. RT-qPCR amplification of *Mycoplasma pneumoniae* DNA in the patient oro-nasopharyngeal sample

A lumber puncture was performed due to the patient's deteriorating condition. The CSF had a xanthochromic appearance. The biochemical analysis of the cerebrospinal fluid (CSF) revealed an elevated total protein and slightly low sodium levels, while glucose, potassium, and chlorine were within the normal range (Table 1). Cellular analysis of the CSF revealed a 73/mm^3 leukocyte count with 25% monocytes and 75% polymorphonuclear neutrophils (PMNs). Direct microscopy of the CSF sample indicated no pleocytosis or bacteria, and the CSF culture did not present any microbial growth. CSF adenosine deaminase test for tuberculous meningitis (<1.00, normal range: 0.00-6.00 U/L) as well as herpes simplex virus type-1 IgM, varicella zoster virus IgM and *Borrelia burgdorferi* IgM in CSF were also negative. *M. pneumoniae* was not detected in the CSF sample using PCR. On day 4 of admission, the patient's CRP levels were high (5.41 mg/dL, normal range: 0.00-0.50 mg/dL), which was reduced (1.43 mg/dL, normal range: 0.00-0.50 mg/dL) on day 7. In addition, a high D-dimer coagulation test result was noted (511 ng/mL, normal range: 0-250 ng/mL).

Table 1. Biochemical analysis of the patient's cerebrospinal

Test	Patient CSF	Reference
Glucose (mg/dL)	56	40-70
Total protein (mg/dL)	49,7	15-45
Sodium (mmol/L)	139	142-150
Potassium (mmol/L)	3,0	2,2-3,3
Chlorine (mmol/L)	124	118-132
LDH (U/L)	<30	<40

LDH: Lactate dehydrogenase, CSF: cerebrospinal fluid

A limbic encephalitis panel was also performed as it could not be ruled out. This panel included anti-glutamate type AMPA1 and AMPA2, anti-CASPR2, anti-LGI1, anti-GABAB (B1-B2), anti-Dppx, and NDMA receptor antibody tests, and all of the test results were negative. Oligoclonal band electrophoresis investigation of the CSF was negative, although matching oligoclonal bands in BOS and serum were observed which indicates a systemic immune reaction which was not intrathecal. IgG levels in serum were normal (10.21 g/L, normal range: 6.50-16.00 g/L), while IgG levels in CSF were detected to be elevated (9.34 mg/dL, normal range: 3.30-6.10 mg/dL). Anti-myelin oligodendrocyte glycoprotein (MOG) IgG and neuromyelitis optica- aquaporin 4 IgG were also negative.

Cranial MRI imaging revealed a well-defined, oval-shaped lesion, approximately 10x8x7 mm in size, at the midline level of the splenium of the corpus callosum (Fig. 2). Hyperintense signals were observed in the T2-weighted images in axial and sagittal planes (a, b), and hypointense signals in the contrast-enhanced T1-weighted images in the axial plane (c). Hyperintensity was observed in the diffusion-weighted image (d), while in the apparent diffusion coefficient (ADC) map (e), hypointensity indicating diffusion restriction was detected.

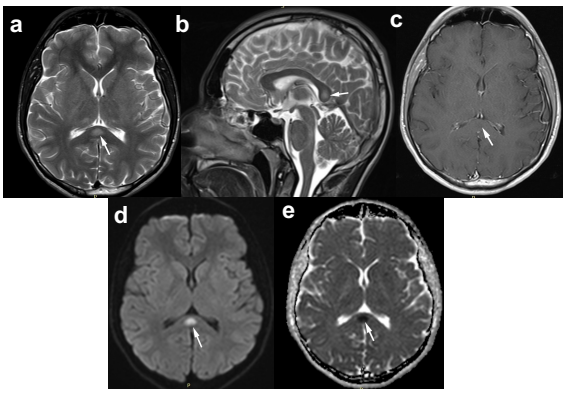

Fig. 2. Brain magnetic resonance imaging of the patient. A well-defined, oval-shaped lesion (white arrows), approximately 10x8x7 mm in size, is observed at the midline level of the splenium of the corpus callosum. Hyperintense signals are seen in the T2-weighted images in axial and sagittal planes (a, b), and hypointense signals in the contrast-enhanced T1-weighted images in the axial plane (c); however, no significant contrast enhancement is detected in the lesion. In the diffusion-weighted image (d), hyperintensity is observed, while in the apparent diffusion coefficient (ADC) map (e), hypointensity indicating diffusion restriction is detected

Upon admission of the patient to the ward, intravenous ceftriaxone 2x2 g, oral doxycycline 2x100 mg, and intravenous acyclovir 3x750 mg were administrated for encephalitis and atypical pneumoniae pre-diagnosis. A single dose of hydroxocobalamin was also administered. Since the patient experienced vomiting following the administration of doxycycline and could not tolerate the drug, doxycycline was discontinued, and he was given intravenous moxifloxacin 1x400 mg. He did not have a fever during follow-up. On day 2 of admission, symptoms improved significantly. Upon the molecular diagnosis of *M. pneumoniae*, acyclovir and ceftriaxone were discontinued. On day 4 of admission, 4000 units of enoxaparin sodium were given to the patient subcutaneously. The patient woke up spontaneously, without any stimulant, on the 4th day of treatment The nystagmus in his right eye continued but improved on day 6 of admission. On the 7th day of hospitalization, the patient's clinical condition improved, and he was discharged on oral moxifloxacin on the patient's consent.

3. Discussion

MERS is characterized by acute mild symptoms of encephalopathy, which presents with changes in the corpus callosum observed within the brain MRIs, and recovery is possible without treatment. MERS is known to have two types: type 1, in which damage is limited to the corpus callosum on MR imaging, and type 2, where the damage is spread to the entire corpus callosum or adjacent white matter or both (6). Among the two types, type 1 MERS is reported more commonly.

The prevalence of MERS is noticeably higher in the pediatric population, although a number of cases have also been reported in adults. The most common causative agents associated with MERS include influenza A and B, rotavirus, adenovirus, respiratory syncytial virus, and herpes simplex virus, while bacterial etiologies such as *E. coli* O-157, *S. pneumoniae*, *Salmonella typhi,* and Legionella have been previously reported (7). The current case report diagnosed the patient with MERS associated with *M. pneumoniae* infection using syndromic molecular testing (PCR) and cranial MR imaging. Although scarce, a limited number reports of MERS associated with *M. pneumoniae* exist in literature. Talukder et al. reported a 5-year-old African-American boy presenting with an acute onset intractable vomiting, diarrhea and, abnormal tensing movements, high fever, encephalopathy, and his brain MRI demonstrated a T2 fluid-attenuated inversion recovery sequence hyperintensity in the splenium of the corpus callosum. This patient was treated with a single pulse dose of intravenous methylprednisolone with a complete resolution of findings. He completed 5 days of glycopeptide and beta-lactam antibiotics as in-patient and was later discharged home without antibiotics (7). On the contrary, in our case study, methylprednisolone was not administered, and the patient was treated with moxifloxacin 1x400 mg IV upon diagnosis of M. pneumoniae. The patient was also given 4000 units of enoxaparin sodium subcutaneously as an anticoagulant, which was not given in the case described by Talukder et al. (7). In a separate study, Yuan et al. described two cases of MERS, infected with *M. pneumoniae* aged 9 and 12, who were both found to be negative for meningeal irritation and bilateral Babinski's signs. While both patients showed poor mental status in neurological examination, interestingly, one of the patients had mouth drooping on the right side and shallow nasolabial sulcus on the left side due to left peripheral facial paralysis, known to be associated with *M. pneumoniae* infection. Both cases showed a focal high-signal lesion in the splenium of the corpus callosum in cranial MRI and were treated with 10 mg/kg/day azithromycin for 5 days as well as mannitol 5 ml/kg 8 hourly to decrease the intracranial pressure. Both patients had full recovery within 10 days (8). Alternatively, in the current case study, although acyclovir was also used prior to the confirmation of *M. pneumoniae* infection, antibacterial therapy was given as moxifloxacin for 7 days instead of azithromycin for 5 days. No drugs were administered to decrease the intracranial pressure in our case report. In a more recent study in 2020, Sadohara et al. reported an adult case of *M. pneumoniae*-associated with MERS who was treated with levofloxacin parenterally as well as prednisolon, gaining consciousness by day 6 of hospital admission. In this study, the authors also provided a comprehensive review of

literature providing a list of adult MERS cases associated with *M. pneumoniae* comprised of eleven patients ages 17-45 years, six males and five females. In this review, initial symptoms included high fever in all cases as well as CNS manifestations varying from mild symptoms such as headache, vertigo, blurred vision and disturbance of consciousness to meningeal signs such as limb weakness and seizures. Similarly, in our case report, the patient also had the initial symptoms, including headache and fever, and later developed a tendency to sleep, loss of consciousness, and nystagmus. In the study by Sadohara et al., the possible pathogenesis of CNS manifestations of *M. pneumoniae* infection was classified into three overlapping pathomechanisms: a direct type with neural damage due to cytokines, a vascular occlusion type with vasculitis and thrombosis or vasculopathy and embolism, or an indirect type due to autoimmunity (9).

Although neuroimaging is vital for MERS diagnosis, laboratory tests remain crucial for a confirmed diagnosis of *M. pneumoniae*-associated MERS. Enzyme-linked immunosorbent assays (ELISAs) for the detection of *M. pneumoniae*-specific antibodies in serum and PCR for the detection of *M. pneumoniae* DNA in the pharyngeal and CSF specimens are widely used techniques in diagnosis. The combination of PCR and serological testing has been proposed to yield more reliable results, although *M. pneumoniae* in CSF was reported to be undetectable by PCR in some patients, similar to the case presented in the current study (10). In the current case, serological testing was not available and, therefore, was not performed.

In conclusion, we reported an adult case of type I MERS, which is associated with *M. pneumoniae*. This study enriched the available literature on MERS pathogens and provided valuable data for the diagnosis of the syndrome for clinicians. As a rare condition which can be missed by clinicians, rapid molecular diagnosis of the etiological agent and early diagnosis of the MERS syndrome can ensure good prognosis and prevent overtreatment in these patients. As different studies report diverse treatment strategies, controlled trials may be beneficial in assessing the effectiveness of therapeutic methods in MERS cases.

Conflict of interest

The authors declared no conflict of interest.

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None to declare.

Authors' contributions

Concept: H.A., B.B., K.S., Design: H.A., B.B., K.S., Data Collection or Processing: H.A., T.A., Y.D., G.K., Analysis or Interpretation: H.A., B.B., K.S., Literature Search: H.A., B.B., T.A., Y.D., K.S., G.K., Writing: H.A., B.B., T.A., Y.D.

Ethical Statement

Thıs study does not requıre ethıcs commıttee approval.

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