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Case of clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS) due to *Legionella* pneumonia

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SUMMARY

Clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS) is a clinicoradiologic syndrome diagnosed by temporary hyperintense lesion in the area, including the splenium of the corpus callosum, on diffusion-weighted imaging and neuropsychiatric symptoms that recover without sequelae. MERS is rare in adults, especially elderly people. We herein report a man in his 60s diagnosed with MERS caused by *Legionella* pneumonia. He completely recovered with only the administration of levofloxacin and azithromycin despite the risk factors of an advanced age, medical history of untreated hypertension, bilateral spontaneous pneumothoraxes, smoking and drinking habits and pulmonary emphysema. To our knowledge, this is the oldest case of MERS due to *Legionella* pneumonia and extremely old among total MERS cases. Our research revealed that *Legionella* species are the most common pathogens of adult-onset MERS, while viruses are the main causative factors in children. This case helps clarify the features of MERS in high-risk adults.

BACKGROUND

Clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS) is a clinicoradiologic syndrome characterised by distinctive MRI findings and central nervus system manifestations with a good prognosis.[1 2] The MRI finding of MERS is a reversible lesion with transiently reduced diffusion in the corpus callosum involving at least the splenium of the corpus callosum (SCC).[1] Common neurological symptoms are delirious behaviour, consciousness disturbance and seizures,[1] with headache, somnolence, ataxia, dysarthria and blurred vision also observed.[3] Both SCC lesions on MRI and neuropsychiatric manifestations completely disappear typically within a month.[1 2] MERS is predominantly caused by a viral infection and is mainly seen in children,[1 2] with adult-onset MERS cases being relatively uncommon and elderly-onset cases quite rare. The features of adult-onset MERS have barely been explored.

We here report a case of *Legionella* pneumonia-associated MERS in elderly man. In connection with this case, we discuss differences in the aetiology of MERS between children and adults and highlight interesting common features of MERS and Legionnaires' disease that may help clarify the pathophysiology of both diseases.

There are no competing interests relevant to this report for any authors.

CASE PRESENTATION

A man in his 60s visited our hospital because of a feeling of weakness in both lower limbs for the last 3 days. He had gone to a hot spring facility 5 days before the visit. His medical history was bilateral spontaneous pneumothoraxes and untreated hypertension. He did not have a family doctor and was on no other regular medications apart from vitamin tablets. He was a current 40 pack/year smoker and had an alcohol intake of 300 mL of shochu and 350 mL of beer daily.

He did not have a high fever, but our initial observation revealed a temperature of 39.1°C. Other vital signs were a blood pressure of 198/94 mm Hg, heart rate of 115 bpm, respiration rate of 22/min and oxygen saturation was 95% on room air. An ECG showed 109 bpm, unregular rhythm and atrial fibrillation. A neurological examination revealed mild disturbance of consciousness (Japan Coma Scale I-1, Glasgow Coma Scale E4V4M6), dysarthria, kinetic tremor in both hands and a gait disorder. His manner of speaking was slightly unsmooth. He demonstrated inattentiveness and was also slightly hyperactive. He was able to follow commands mostly, but delirious behaviour, such as removing his oxygen mask was observed. He did not show any response to specific stimuli.

INVESTIGATIONS

His blood test showed a severe inflammatory response, elevated liver enzymes, electrolyte abnormalities and CK 1551 IU/L. *Legionella pneumophila* (subtype 1) urinary antigen was positive (table 1). Meanwhile, sputum culture of Legionella pneumophila was negative.

Initial chest X-ray showed consolidation in the right lower lobe. Chest CT also showed consolidation in the right inferior lobe and pulmonary emphysema in both lungs (figure 1). Given these findings as well as the urinary positivity for *Legionella pneumophila* antigen, he was diagnosed with *Legionella* pneumonia and admitted. To examine his consciousness disorder, head CT and MRI were performed on the admission day. Head CT findings were normal. MRI of the brain revealed an abnormal hyperintensity in the SCC on diffusion-weighted imaging (DWI). The same area also showed slight hyperintensity on T2-weighted imaging (T2WI)

Table 1 Laboratory data on admission

(Complete blood count)		(Diabetology)	
WBC	13.7x10^9/L	HbA1c (NGSP)	5.8%
Neu	91.40%	Glucose	143 mg/dL
RBC	4.48x10^12/L		
Hb	144 g/L	(Coagulation test)	
Ht	39.60%	PT	11.6 s
Plt	22.0×10⁴/μL	PT_INR	0.99
		APTT	33.1 s
(Biochemistry)		D-dimer	3.6 μg/mL
TP	6.5 g/dL		
Alb	3.0 g/dL	(Infections)	
AST	91 U/L	Influenza A antigen	(–)
ALT	63 U/L	Influenza B antigen	(–)
ALP	62 U/L	SARS-CoV-2 antigen	(–)
T-Bil	1.2 mg/dL	SARS-CoV-2 nucleic acid	(–)
Ch-E	209 U/L		
LDH	343 U/L	(Urinalysis)	
γ-GTP	56 U/L	pH	5.0
S-AMY	48 U/L	Pro	(3+)
P-AMY	22 U/L	Bld	(3+)
CK	1551 U/L	Ket	(1+)
UN	23.1 mg/dL	Bil	(–)
Cr	1.55 mg/dL	Glu	(–)
UA	6.0 mg/dL	Coccus	(+)
Na	131 mmol/L	*Legionella pneumophila*	
K	3.8 mmol/L	urinary antigen	(+)
Cl	97 mmol/L	Pneumococcus capsule	(–)
Ca	7.9 mg/dL		
CRP	33.83 mg/dL		
eGFR	36.2 mL/min/1.73 m^2		

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cr, creatinine; CRP, C reactive protein; eGFR, estimated glemerular filtration rate; LDH, lactate dehydrogenase; P-AMY, pancreatic amylase; RBC, red blood cell; S-AMY, serum amylase; TP, toral serum protein; UA, urinary acid; WBC, white blood cell.

and fluid-attenuated inversion recovery (FLAIR) imaging. MR angiography did not show any obvious abnormality abnormalities (figure 2A–C). An apparent diffusion coefficient map was not performed. Patients with Legionnaires' disease often present with a high fever, headache, altered mental status and leukocytosis. Once Legionnaires' disease has been diagnosed, a cerebrospinal fluid (CSF) test is not very informative for the treatment, so we did not perform a CSF test. Electroencephalography was also unexamined.

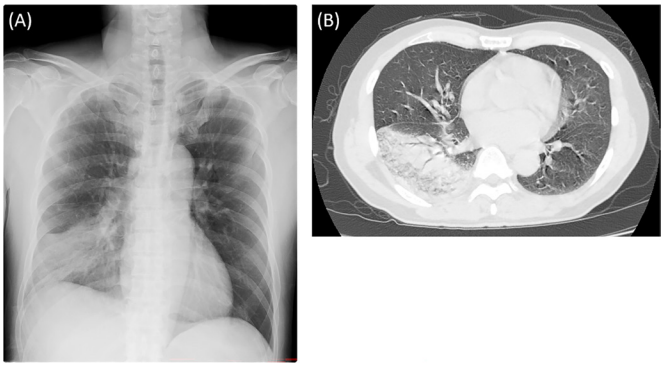

Figure 1 Chest X-ray and chest CT on admission. (A) Chest X-ray. Consolidation in the right inferior lobe. (B) Chest CT. Consolidation in the right inferior lobe.

DIFFERENTIAL DIAGNOSIS

Cerebral infarction was excluded because both the clinical symptoms and abnormal hyperintense lesion in the SCC on DWI and T2WI disappeared 21 days after hospitalisation. In cases of cerebral infarctions, neurological symptoms usually persist to some extent, and T2WI normally shows hyperintension on day 21.

Brain tumour was excluded because the hyperintense lesion on head MRI completely disappeared.

Mycoplasma pneumonia can cause both pneumonia and MERS. However, *L. pneumophila* antigen was positive in the patient's urine. His imaging and laboratory findings and history of visiting a hot spring profoundly indicated *Legionella* pneumonia.

TREATMENT

We administered 500 mg/day of levofloxacin from hospital days 1 to 8 and 500 mg/day of azithromycin from days 2 to 11. His neuropsychiatric symptoms had resolved on day 5. He recovered from *Legionella* pneumonia and discharged on day 13. Atrial fibrillation was temporary, so we did not administer anticoagulants.

OUTCOME AND FOLLOW-UP

Twenty-one days after admission, we performed follow-up MRI of the brain. The hyperintense lesion in the SCC had resolved on DWI, T2WI and FLAIR imaging (figure 2D–F). We then diagnosed him with MERS. No neurological abnormalities were observed for 6 months after discharge.

DISCUSSION

We encountered a man in his 60s with MERS caused by *Legionella* pneumonia. The disease concept of MERS was first proposed by paediatricians in Japan.[2] It mainly develops in children,[1 2] where the main cause is viral, and its prognosis is good.[1 2 4] We summarised the aetiology of child-onset MERS in several articles we found using the PubMed search engine (see: figure 3A and online supplemental table 1A).[2–9]

Adult-onset MERS, by contrast, is relatively rare, and its main pathogen remains unclear. We also summarised the aetiology of MERS in adults to compare the findings with those in children. In our research, 70 cases of MERS among adult males and females aged 19 and older were reported. Among the 71 cases of adults, including our present case, 27 (38.0%) were caused by bacteria, 16 (22.5%) were caused by viruses, 8 (11.3%) were caused by non-infectious sources and 20 (28.2%) were unidentified. Non-infectious sources include Anti-Yo rhombencephalitis, ipilimumab, C-section, tick-bites, amanita phalloides intoxication, haemolytic uraemic syndrome, acute urinary retention and new-onset refractory status epilepticus. The age range was 19–75 years old, and the mean age was 38.7 years old (see figure 3B and online supplemental table 1B).[3 7 9–16]

Accordingly, it is possible that adult-onset MERS is more likely to be triggered by bacteria than child-onset cases. Indeed, we found 16 cases of *Legionella*-associated MERS (mean age: 49.3 years old).[3 7 10 11] In contrast, no child-onset MERS by *Legionella* species (spp) have been reported. Consequently, *Legionella* spp appear to be the most common pathogens of MERS in adults.

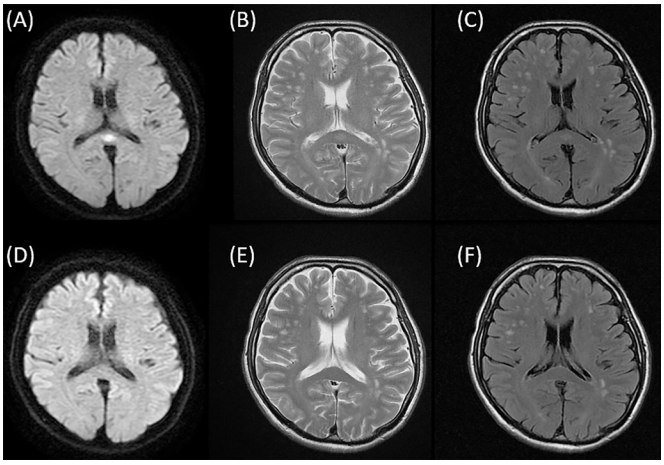

Figure 2 Head MRI on admission and day 21. (A–C) Head MRI on admission day. (A) DWI. Abnormal hyperintensity in the SCC. (B) T2WI. Mild hyperintensity in the SCC. (C) Fluid-attenuated inversion recovery (FLAIR). Mild hyperintensity in the SCC. (D–F) Head MRI on day 21. (D) DWI. Abnormal hyperintensity in the SCC disappeared. (E) T2WI. Hyperintensity in the SCC disappeared. (F) FLAIR. Hyperintensity in the SCC disappeared. SCC, splenium of the corpus callosum; T2WI, T2-weighted imaging.

Our case is the oldest one of *Legionella*-associated MERS and the third-oldest among all 71 total MERS cases we found in our research. The present patient completely recovered with only the administration of antibacterial drugs, despite his risk factors, including an elderly age, smoking history and emphysema. This suggests that MERS retains its reversible characteristic even in high-risk elderly people, so clinicians can select watchful waiting for neurological symptoms and SCC lesions on brain MRI in order to administer the most appropriate treatment for primary illness.

However, several MERS cases in adults were accompanied by severe disease, with intractable cases and one death reported.[12 13] A man in his 70s who developed MERS due to COVID-19 died of respiratory failure despite the improvement of his neurological symptoms.[13] While some adult cases match with MERS findings, there are some differences between adult and paediatric cases with respect to main causative agents, maturity of the brain, underlying health conditions, etc. It is thus possible that neurological abnormalities and hyperintense lesions in the SCC on DWI in mature adults and immature children have differing clinical significance.

Considering that bacteria are the main pathogens of MERS in adults, the imaging and clinical findings may reflect the severity of inflammation. It is difficult to distinguish whether or not the altered mental status is actually related to a brain pathophysiology that causes abnormal callosal signals or reflects a systemic cause of encephalopathy. Once again, it should be noted the fact that the main cause of adult MERS is Legionnaires' disease, an extremely severe bacterial infectious disease with a death rate of 5%–10% overall and 40%–80% in untreated immunosuppressed patients.[17] While the prognosis of MERS is considered to be good, we need to carefully treat the primary illness, manage the general condition and perform cautious observation for neuropsychiatric manifestations and MRI lesions to confirm that the condition is truly reversible. More cases should be gathered to clarify the details of adult-onset MERS, especially elderly cases cases.

Incidentally, the pathophysiology of MERS is unclear. Several mechanisms, such as intramyelinic oedema,[2] inflammatory infiltrate,[2] electrolyte abnormality[18] and oxidative stress,[19] have been suggested, but why lesions arise in the SCC remains unclear, especially since the symptoms of MERS, including delirious behaviour, consciousness disturbance and seizures, cannot be induced by impairment of the SCC.

Here, we considered about the developmental mechanism of neurological abnormalities of MERS and the common points with Legionnaires' disease. Hyponatraemia is sometimes observed in both adult-onset and child-onset MERS cases.[3 18] Hyponatraemia and neurological abnormalities, such as impaired consciousness, are common in Legionnaires' disease too, although the mechanism remains unclear.[20 21] In our case, both hyponatraemia and some neurological abnormalities, including disturbance of consciousness, were observed. Elevation of serum interleukin-6 (IL-6) levels was reported in several child-onset cases of MERS.[3] IL-6 is considered to induce an increase in vasopressin secretion via a non-osmotic pathway and cause hyponatraemia.[22] Lipopolysaccharides, components of the outer membrane of Gram-negative bacteria, including *Legionella* spp, induce IL-6 secretion.[22] Only a few cases of MERS have been evaluated for IL-6, but considering the physiology, IL-6 may be increased in adult *Legionella*-associated MERS

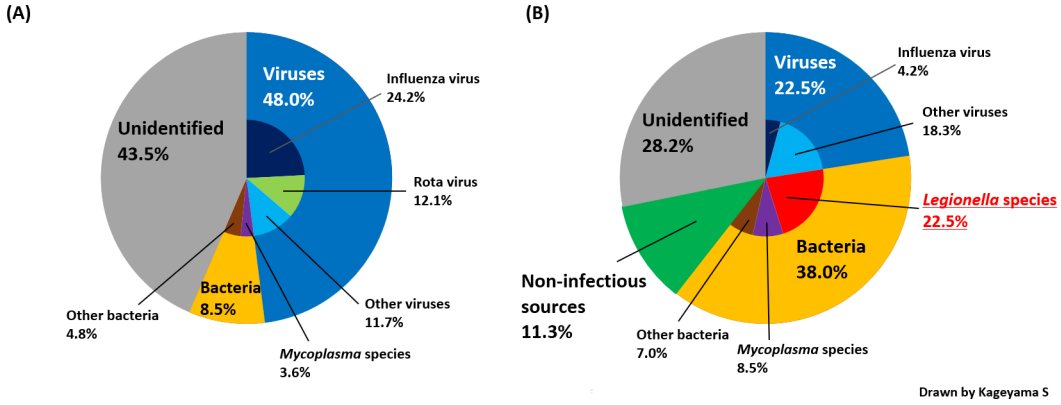

Figure 3 Etiology of child-onset and adult-onset MERS. (A) Etiology of child-onset MERS.[2–9] Number of patients: 248, age range: 0–18 years old. Details in online supplemental table 1A. Coinfection cases included. (B) Etiology of adult-onset MERS, including our case.[3 7 9–16] Number of patients: 71, age range: 19–75 years old, Mean age: 38.7 years old. Details in online supplemental table 1B. These were drawn by SK. MERS, mild encephalitis/encephalopathy with a reversible splenial.

cases. We; therefore, hypothesise that IL-6-induced vasopressin secretion may be involved in the pathogenesis of both MERS and neurological abnormalities of Legionnaires' disease. Further investigations are required to elucidate the details of adult-onset MERS and Legionnaires' disease.

Patient's perspective

I totally recovered. I am happy that I can enjoy my life healthily again.

Learning points

- As described in this case report, a patient with clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS) caused by *Legionella* pneumonia recovered without sequel with only administration of antibacterial drugs, despite risk factors such as an elderly age, smoking history and emphysema.
- Although MERS mainly develops in children, with the most common pathogens being viruses, adult-onset MERS tends to be caused by bacteria, and the most frequent pathogens are *Legionella* species.
- When clinicians suspect MERS, the primary illness should be carefully treated, and watchful waiting for neurological symptoms and MRI findings can be practised.
- As observed in this case, unexplained hyponatraemia and neuropsychiatric abnormalities are common symptoms in both MERS and Legionnaires' disease, so interleukin-6-induced hyponatraemia may be related with both diseases.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

REFERENCES

1 Takanashi J-ichi. Two newly proposed infectious encephalitis/encephalopathy syndromes. *Brain Dev* 2009;31:521–8.
2 Tada H, Takanashi J, Barkovich AJ, *et al*. Clinically mild encephalitis/encephalopathy with a reversible splenial lesion. *Neurology* 2004;63:1854–8.
3 Shi B-C, Li J, Jiang J-W, *et al*. Mild encephalitis/encephalopathy with a reversible splenial lesion secondary to encephalitis complicated by hyponatremia: a case report and literature review. *Medicine* 2019;98:e17982.
4 Hoshino A, Saitoh M, Oka A, *et al*. Epidemiology of acute encephalopathy in Japan, with emphasis on the association of viruses and syndromes. *Brain Dev* 2012;34:337–43.
5 Ka A, Britton P, Troedson C, *et al*. Mild encephalopathy with reversible splenial lesion: an important differential of encephalitis. *Eur J Paediatr Neurol* 2015;19:377–82.
6 Fang Q, Chen L, Chen Q, *et al*. Clinically mild encephalitis/encephalopathy with a reversible splenial lesion of corpus callosum in Chinese children. *Brain Dev* 2017;39:321–6.
7 Yuan J, Yang S, Wang S, *et al*. Mild encephalitis/encephalopathy with reversible splenial lesion (MERS) in adults-a case report and literature review. *BMC Neurol* 2017;17:103.
8 Xue J, Zhang Y, Kang J, *et al*. A cohort study of mild encephalitis/encephalopathy with a reversible splenial lesion in children. *Brain Behav* 2021;11:e2306.
9 Grosset L, Hosseini H, Bapst B, *et al*. Mild encephalopathy with reversible splenial lesion: description of nine cases and review of the literature. *Seizure* 2021;88:83–6.
10 Nishida T, Ishiguro T, Kawate E. A case of a reversible splenial lesion associated with pneumonia caused by Legionella pneumophila serogroup 2 (in Japanese). *Nihon Kokyuki Gakkai Zasshi* 2017;6:417–20.
11 Shimono H, Hoshina Y, Ogawa E, *et al*. A rare etiology of mild encephalitis/encephalopathy with reversible splenial lesion. *Clin Case Rep* 2021;9:e04759.
12 Mizutani AU, Shindo A, Arikawa S, *et al*. Reversible splenial lesion in a patient with new-onset refractory status epilepticus (NORSE). *eNeurologicalSci* 2020;18:100220.
13 Hayashi M, Sahashi Y, Baba Y, *et al*. COVID-19-associated mild encephalitis/encephalopathy with a reversible splenial lesion. *J Neurol Sci* 2020;415:116941.
14 Kakadia B, Ahmed J, Siegal T, *et al*. Mild encephalopathy with reversible splenium lesion (MERS) in a patient with COVID-19. *J Clin Neurosci* 2020;79:272–4.
15 Zhang Y, Shi Q. A wide range of high signal intensities on brain image in adult Mycoplasma pneumoniae-associated mild encephalitis/encephalopathy with a reversible splenial lesion. *Neurol India* 2021;69:1112–3.
16 Hidaka M, Sawamura N, Yokoi M, *et al*. Meningitis retention syndrome associated with complicated mild encephalitis/encephalopathy with reversible splenial lesion in a young adult patient: a case report. *Oxf Med Case Reports* 2021;2021:381–4.
17 The website of World Health organization. Available: https://www.who.int/news-room/fact-sheets/detail/legionellosis [Accessed 24 Oct 2022].
18 Takanashi J-ichi, Tada H, Maeda M, *et al*. Encephalopathy with a reversible splenial lesion is associated with hyponatremia. *Brain Dev* 2009;31:217–20.
19 Miyata R, Tanuma N, Hayashi M, *et al*. Oxidative stress in patients with clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS). *Brain Dev* 2012;34:124–7.
20 Cunha BA, Burillo A, Bouza E. Legionnaires' disease. *Lancet* 2016;387:376–85.
21 Johnson JD, Raff MJ, Van Arsdall JA. Neurologic manifestations of Legionnaires' disease. *Medicine* 1984;63:303–10.
22 Swart RM, Hoorn EJ, Betjes MG, *et al*. Hyponatremia and inflammation: the emerging role of interleukin-6 in osmoregulation. *Nephron Physiol* 2011;118:p45–51.