New Microbes and New Infections 62 (2024) 101543

Contents lists available at ScienceDirect

New Microbes and New Infections

journal homepage: www.journals.elsevier.com/new-microbes-and-new-infections

Letter to the Editor

Challenges in diagnosis of Mediterranean spotted fever in a patient with aseptic meningitis: A case report from Southeast Iran

Dear Editor

Mediterranean spotted fever (MSF), caused by *Rickettsia conorii*, is a tick-borne illness found in the Mediterranean, Black, and Caspian Seas, Sub-Saharan Africa, and the Middle East. Its diverse clinical presentation complicates its diagnosis and management [1]. After an unnoticed tick bite, patients typically develop fever, maculopapular rash, and eschar within 5–7 days. Although asymptomatic infections are common, symptomatic MSF often includes fever, headache, and myalgia. MSF rarely leads to severe complications such as CNS involvement, including aseptic meningitis, particularly in adults [2].

Recent studies have suggested that MSF is endemic in Iran, particularly in southeastern regions [1,3]. We report a case of MSF with aseptic meningitis in a patient from Southeast Iran. This case illustrates the complexities of recognizing and managing MSF, particularly in cases complicated by aseptic meningitis.

On April 20, 2024, an 85-year-old woman from Jiroft, Kerman Province, Southeast Iran, presented to Afzali Hospital with a weeklong fever, chills, weakness, abdominal pain, diarrhea, vomiting, and headache. She had hypertension, a history of cerebrovascular accident (CVA), and no insect bite recall. Her vital signs were as follows: temperature, 39 °C; heart rate 105–130 bpm, blood pressure, 140/85 mmHg; and oxygen saturation, 95 %. A physical examination did not reveal any additional significant findings.

At the initial hospitalization, cerebrospinal fluid (CSF) analysis revealed white blood cells (WBC) 108 with 67 % Polymorphonuclear (PMN) and 33 % lymph a protein level of 137 mg/dL (RR: 15–45 mg/dL) and a glucose level of 71 mg/dL (RR: 50–80 mg/dL). Blood and CSF cultures were negative, although the CSF protein levels were elevated.

On the first day of hospitalization, a series of diagnostic tests were conducted, including a spiral chest CT scan; ultrasound of the kidneys, urinary tract, abdomen, liver, gallbladder, and spleen; and echocardiography. All results were within the normal limits. Laboratory tests upon admission revealed the following: Hemoglobin: 11.5 g/dL (reference range [RR]: 13.8–17.2 g/dL), Leukocyte count: 7500 cells/mm^3 (RR: 4500–11,000 cells/mm^3), Platelet count: 71 x 10^3 cells/mm^3 (RR: 150-450 x 10^3 cells/mm^3), Serum creatinine: 0.8 mg/dL (RR: 0.8–1.2 mg/dL), Urea: 22 mg/dL (RR: 6–24 mg/dL), Alanine aminotransferase (ALT): 60 U/L (RR: 29–33 U/L), Aspartate aminotransferase (AST): 80 U/L (RR: 8–33 U/L), Alkaline phosphatase (ALP): 220 U/L (RR: 44–147 U/L), Prothrombin Time (PT): 14.9 seconds (RR: 11–13.5 seconds), Partial Thromboplastin Time (PTT): 48 seconds (RR: 25–35 seconds), Lactic acid dehydrogenase (LDH): 302 U/L (RR: 135–214 U/L), Creatine phosphokinase (CPK): 205 U/L (RR: 30–135 U/L), Erythrocyte sedimentation rate (ESR): 37 mm/hr (RR: <30 mm/hr), C-reactive protein (CRP): 80 mg/dL (RR: <0.3 mg/dL). Her platelet count was lower than normal but began to increase during hospitalization and treatment. ALT, AST, ALP, LDH, PT, PTT, ESR, and CRP levels were also elevated (Table 1). The patient's red blood cell (RBC) count on the first day of hospitalization was 4.3 mcL (RR: 4.35–5.65 mcL), with a declining trend observed during her stay (Table 1). The hemoglobin and hematocrit (HCT) levels also showed a decreasing trend. The PT and PTT values fluctuated throughout hospitalization.

An abdominopelvic computed tomography (CT) scan showed no abnormalities despite persistent abdominal pain. The patient later developed a red maculopapular rash, thrombocytopenia, and declining consciousness, which prompted ICU transfer.

On April 30, 2024, a blood sample was sent to the Research Center for Emerging and Reemerging Diseases at the Pasteur Institute of Iran to detect a *Rickettsia* infection, following the physician's suspicion. An IFA test (Vircell, Spain) revealed an anti-*R.* conorii IgM titer of 1:1536 and IgG titer of 1:640. However, quantitative real-time polymerase chain reaction (qPCR) targeting the 16S rRNA gene in blood samples yielded negative results for *Rickettsia* spp., suggesting an absence of pathogens in the bloodstream. Based on clinical symptoms and laboratory findings, the patient was diagnosed with MSF and treated with il oral doxycycline and intravenous (IV) levofloxacin.

Due to her inability to take oral doxycycline, the medication was administered via gavage, and a second blood sample, sent on May 6, 2024, to the same research center, indicated MSF through a significant increase in IgG titer (1:2560) detected one week after the initial IFA test. The paired serum specimens tested positive for *R. conorii* by the IFA assay, and by May 2024, the patient's condition had improved, and she was discharged in relatively good general health.

The incidence of MSF is influenced by seasonal and geographical factors, with southeastern Iran being a key area of concern. This case, presented in April, highlights the seasonal nature of MSF as tick activity increases with rising temperatures, emphasizing the need for heightened awareness and preventive strategies [1]. Early diagnosis of MSF in our case was challenging because of the limited sensitivity of the initial diagnostic tests, causing delays and increasing the risk of complications such as aseptic meningitis. Seroconversion typically occurs 7–15 days post-symptom onset, further complicating its detection [4]. Prompt treatment is crucial to prevent severe complications and fatal outcomes, especially in endemic areas. In our case, doxycycline and levofloxacin were administered before the diagnosis, leading to significant improvement. Doxycycline is the primary treatment [4], but levofloxacin is also effective [5]. This case emphasizes the importance of early treatment based on clinical judgment, especially when aseptic meningitis and varied symptoms suggest a rickettsial infection.

https://doi.org/10.1016/j.nmni.2024.101543
Received 22 October 2024; Received in revised form 26 November 2024; Accepted 27 November 2024
Available online 28 November 2024

Table 1
Laboratory findings of MSF case during hospitalization.

Days (hospitalization)/blood analysis	1	3	4	6	7	8	9	10
RBC (mcL)	4.3	4.3		3.36	3.2	3.12[b]	2.95[b]	2.94[b]
White blood cell (× 109/L)	7.5	6.5	–	11.4	10	8.4	6.7	6.5
Hemoglobin (g/dl)	11.5[b]	11.8[b]	–	9.6[b]	8.8[b]	8.5[b]	8.2[b]	8[b]
mean corpuscular hemoglobin (pg/cell)	27.2[b]	27.2[b]	–	26.8[b]	27.6	27.2	26[b]	27.2
mean corpuscular volume (fl)	86.6	86.6	–	86	85.6	88.5	88	85.7
HCT	29.8[b]	–	–	–	–	27.6[b]	26[b]	25.2
Alanine aminotransferase (U/L)	60[a]		–	–	–	–	–	–
Plt (cells/mm^3)	71[b]	64[b]	–	132[b]	144	158	174	158
ALK-ph	220[a]	–	–	–	–	–	–	–
LDH	302[a]	–	–	–	–	–		–
Cpk	205[a]	–	–	–	–	–	–	–
Lymphocyte	16.3[¥]	–	–	16[b]	–	–	–	–
Erythrocyte Sedimentation Rate (mm/hour)	37[a]	–	–	–	–	–	–	–
C-Reactive Protein (mg/dL)	81[a]	–	–	–	–	–	–	–
Urea	34	–	–	–	–	–	29	–
Cr	0.8		–	–	–	–	0.6	–
B/c	neg	–	–	–	–	–	–	–
U.c.	neg	–	–	–	–	–	–	–
CSF culture	neg	–	–	–	–	–	–	–
CSF WBC	108[a]	–	–	–	–	–	–	–
CSF PMN	67	–	–	–	–	–	–	–
CSF lymph	33	–	–	–	–	–	–	–
CSF glucose	71	–	–	–	–	–	–	–
CSF prot	137[a]	–	–	–	–	–	–	–
PT	14.9	–	–	–	29[a]	13	20[a]	33[a]
PTT	48	–	–	–	13.7[b]	35	>120[a]	>120[a]

[a] Increased.
[b] Decreased, -not detected, neg: negative.

Consent for publication

The patient gave written informed consent for their personal or clinical details and any identifying images to be published in this study.

CRediT authorship contribution statement

Mehrdad Farokhnia: Writing – review & editing, Writing – original draft, Methodology. **Safoura MoradKasani:** Writing – review & editing, Writing – original draft, Methodology. **Ehsan Mostafavi:** Writing – review & editing. **Saber Esmaeili:** Writing – review & editing, Supervision.

Clinical trial number

Not applicable.

Availability of data and materials

All data generated or analyzed in this study are included in this published article.

Funding

Not applicable.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We would like to thank Kerman University of Medical Sciences for their help with data collection.

Abbreviations

MSF: Mediterranean spotted fever; CNS: Central nervous system; IFA: Indirect immunofluorescence; CVA: Cerebrovascular accident; WBC: White blood cells; PMN: Polymorphonuclear; RBCs: red blood cells; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; PT: Prothrombin Time; PTT: Partial Thromboplastin Time; LDH: Lactic acid dehydrogenase; CPK: Creatine phosphokinase; CSF: Cerebrospinal fluid; RBC: Red blood cell; HCT: Hemoglobin and hematocrit; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; qPCR: Quantitative real-time polymerase chain reaction; IV: Intravenous.

References

[1] Farrokhnia M, Ghalejoogh ZY, Rohani M, Ghasemi A, Esmaeili S, Mostafavi E. Cases of Mediterranean spotted fever in southeast of Iran. Iran J Microbiol 2020;12(3):256–60.
[2] Tikare NV, Shahapur PR, Bidari LH, Mantur BG. Rickettsial meningoencephalitis in a child–a case report. J Trop Pediatr 2010;56(3):198–200.
[3] Baseri N, Salehi-Vaziri M, Mostafavi E, Bagheri Amiri F, Latifian M, Stenos J, et al. Investigation of Rickettsia conorii in patients suspected of having Crimean-Congo hemorrhagic fever. Pathogens 2022;11(9):973.
[4] Spernovasilis N, Markaki I, Papadakis M, Mazonakis N, Ierodiakonou D. Mediterranean spotted fever: current knowledge and recent advances. Trav Med Infect Dis 2021;6(4).
[5] Maurin M, Raoult D. Bacteriostatic and bactericidal activity of levofloxacin against Rickettsia rickettsii, Rickettsia conorii,'Israeli spotted fever group rickettsia'and Coxiella burnetii. J Antimicrob Chemother 1997;39(6):725–30.

Mehrdad Farokhnia[1]
Research Center for Hydatid Disease in Iran, Kerman University of Medical Sciences, Kerman, Iran

Safoura MoradKasani[1]
Department of Epidemiology and Biostatics, Research Centre for Emerging and Reemerging Infectious Diseases, Pasteur Institute of Iran, Tehran, Iran
Pasteur Institute of Iran, Tehran, Iran

Ehsan Mostafavi
Department of Epidemiology and Biostatics, Research Centre for Emerging and Reemerging Infectious Diseases, Pasteur Institute of Iran, Tehran, Iran

National Reference Laboratory for Plague, Tularemia and Q Fever, Research Centre for Emerging and Reemerging Infectious Diseases, Pasteur Institute of Iran, Akanlu, Kabudar Ahang, Hamadan, Iran

Saber Esmaeili*

Department of Epidemiology and Biostatics, Research Centre for Emerging and Reemerging Infectious Diseases, Pasteur Institute of Iran, Tehran, Iran
Pasteur Institute of Iran, Tehran, Iran

National Reference Laboratory for Plague, Tularemia and Q Fever, Research Centre for Emerging and Reemerging Infectious Diseases, Pasteur Institute of Iran, Akanlu, Kabudar Ahang, Hamadan, Iran

* Corresponding author.
E-mail addresses: dr.saberesmaeili@gmail.com, s-esmaeili@pasteur.ac.ir (S. Esmaeili).
Handling Editor: Patricia Schlagenhauf

[1] Mehrdad Farrokhnia and Safoura MoradKasani contributed equally to this paper and should be considered co-first authors.