

# ANDISCRIMINATED ASEPTIC MENINGITIS CASE BETWEEN RICKETTSIA AND LEPTOSPIRAL MENINGITIS

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Rickettsial meningitis and leptospiral meningitis should be included in the differential diagnosis of aseptic meningitis in patients exposed to endemic areas. In this report we describe a case of aseptic meningitis in which neither a rickettsial nor leptospiral etiology could be established.

**Key words:** Meningitis, leptospira, rickettsia

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## INTRODUCTION

Leptospirosis is a zoonosis, caused by infection with pathogenic spirochetes of genus *Leptospira*. Most human infections are probably asymptomatic; the spectrum of illness is extremely wide, ranging from undifferentiated febrile illness to meningitis and severe multisystem disease with high mortality rates. In endemic populations a significant proportion of all aseptic meningitis cases may be caused by leptospiral infection. Human infections are endemic in most regions of Turkey and *L. interrogans* serovar Icterohaemorrhagiae, *L. kirschneri* serovar Butembo, *L. interrogans* serovar Grippotyphosa are prevalent pathogenic leptospiral serovars in Turkey. (1-3). The majority of leptospirosis cases are diagnosed by serology. The most useful test for diagnosis of leptospirosis is the microscopic agglutination test (MAT) because of its high sensitivity and specificity. Cross-reactive antibodies may be associated with syphilis, relapsing fever, lyme disease, viral hepatitis, human immunodeficiency virus infection, legionellosis, and autoimmune diseases (2, 4). Locally isolated strains, which often increase the sensitivity of the test compared with reference strains, can also

be included in the battery of antigens. However, the range of serovars should not be limited to local strains in case the infection is due to a rare serovar or perhaps to a strain that is currently unknown in the region concerned. For this reason too, a saprophytic strain is included (*L. biflexa* serovar Patoc) which cross-reacts with human antibodies generated by a number of pathogenic serovars. Ideally, as with other serological tests, two consecutive serum samples should be examined to look for seroconversion or a four-fold or greater rise in titre. Often only a single serum sample is submitted, possibly from the early phase of the disease. The significance of titres in single serum specimens is a matter of considerable debate, and in different areas, different titres (cut-off points) may be applied. Some consider a titre of 1:100 positive, whilst others accept 1:200, 1:400 or 1:800 as diagnostic of current or recent leptospirosis. However, suggestive evidence for recent or current infection includes a single titer of at least 1:100 obtained after the onset of symptoms (4, 5). Rickettsial infections are divided into two groups: spotted fever group and typhus group. The spotted fevers comprise a large group of tick-, mite- and

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flea-borne zoonotic infections. These include Rocky Mountain spotted fever, *Rickettsia conorii* infections etc. *R. conorii* infection has been designated by many geographic names: Marseilles fever, Mediterranean fever etc. (6, 7). Meningitis signs were seen in the progress of rickettsiosis. Mediterranean spotted fever was endemic in Mediterranean countries including Turkey. In one seroprevalence study that performed in Turkey, antibody to *R. conorii* was positive at 13.27% in 98 healthy persons (8).

In this report, we describe a case of aseptic meningitis in which neither a rickettsial nor leptospiral etiology could be established.

### CASE

A 29 years old woman was admitted to our hospital with a 1-day history of fever, chills, rigors, headache, and disorientation. She was a farmer and living in a rural area. On medical history she had a convulsion episode six years ago. On physical examinations, blood pressure was 120/80 mm Hg, pulse rate was 144 beats per min, and body temperature was 37.5 °C. She was unconscious (Her Glasgow coma score was 11). Neurological examination showed signs of meningeal irritation, including cervical rigidity, Brudzinski's sign and Kerning's sign. She had diffuse petechial rash on the trunk, lower and upper extremities. Abnormal laboratory findings were a leukocyte count of 13 200/mm<sup>3</sup>, with 91% neutrophils, a hemoglobin level of 10.7 g/dl, a platelet count 51000/mm<sup>3</sup>, a glucose level of 60 mg/dl, a blood urea nitrogen level of 24 mg/dl, a creatinine level of 2.9 mg/dl, a c-reactive protein level of 200 mg/l, an alanine amino transferase level of 231 U/l, an aspartate amino transferase level of 56 U/l, a total bilirubin level of 2.2 mg/dl, a lactate dehydrogenase level of 1327 U/l, a creatin phosphokinase level of 4201 U/l. Her prothrombin time was 45.7 seconds, activated partial thromboplastin time was 150 seconds, and international normalized ratio was 5.37. Cranial computerize tomography (CT) revealed diffuse edema. Her cerebrospinal fluid (CSF) contained 70 cells/mm<sup>3</sup>, which consisted of 40 monocytes and 30 neutrophils/mm<sup>3</sup>, 46 mg/dl of sugar, and 106 mg/dl of protein. After blood and CSF cultures were drawn; combination therapy

with intravenous ceftriaxone 2 grams twice daily, intravenous acyclovir 750 mg three times daily, doxycycline 100 mg twice daily by nasogastric tube was started as empirical therapy with the diagnosis of meningitis and leptospirosis. On the 2nd day of treatment, ceftriaxone treatment was stopped and meropenem treatment was started because of general clinical presentation of the patient worsened. Doxycycline and acyclovir treatment was continued. Clinical response was observed on the 5th day of treatment. Seventh day of the treatment, leptospira microagglutination titre to *Leptospira biflexa* serovar Patoc was positive at 1:100. Weil-Felix tests were found to be positive at 1:80 ( $\leq$ 1:180 normal), 1:20 ( $\leq$ 1:180 normal), 1:2560 ( $\leq$ 1:180 normal) titres for *Proteus* OX19, OXK, and OX2, respectively. *Rickettsia* IgG antibodies were positive at >1:128 titre with indirect immunofluorescence assay (Focus Technologies, Cypress, CA, USA). After these results were obtained, acyclovir therapy was stopped on the 7th day of treatment and doxycycline treatment was continued to the 10th day of the treatment. Meropenem treatment was continued to the 14th day of the treatment because we took good result after adding meropenem to treatment. Her general condition was good and vital signs were generally normal but urinary incontinence was still present at the end of the treatment. The patient was discharged from the hospital with calling for control after one week but she didn't come back for control. Blood and CSF cultures were remained negative for bacterial growth.

### DISCUSSION

In rickettsial infection, involvement of the palms and soles is considered characteristic, yet it occurs in only 36% to 82% of patients who have a rash. Careful clinical examination may reveal a tache noire, that is, the eschar at the site of the bite. However, sometimes the eschar may be absent. Also, the frequent absence of a history of tick bite is likely due to transmission by immature larvae and nymphs, which are often noticed (7, 8). In our patient, involvement of the palms and soles and a history of tick bite were absent. The white blood cell count is generally normal in rickettsiosis. Anemia is observed in 5% to 30%.

Thrombocytopenia occurs in more severe cases, but also in some patients with mild disease. Increased concentrations of serum lactate dehydrogenase, creatine kinase, and other enzymes are related to diffuse tissue injury such as multifocal rhabdomyonecrosis. All of these findings were observed in our patient, but these findings may be observed in leptospirosis (4, 7).

Leptospiral meningitis may occur in up to 80% of cases. Symptomatic patients present with an intense, bitemporal and frontal throbbing headache with or without delirium. A lymphocytic pleocytosis occurs, with total cell counts generally below 500/mm<sup>3</sup>. CSF protein levels are modestly elevated between 50 and 100 mg/ml; CSF glucose concentration is normal. In rickettsial meningitis CSF profiles were similar to those of leptospirosis, viral and tuberculous meningitis (2, 9). In our patient, the findings of CSF were compatible with both leptospiral and rickettsial meningitis. In rickettsial infections, indirect immunofluorescence assay (IFA) was used for confirmation of the diagnosis, but it does not allow discrimination of the particular causative spotted fever group *Rickettsia* spp. unless cross-absorption with appropriately selected antigens is performed. Weil-Felix test has lacks sensitivity and specificity. The diagnostic titer is 1:64 for indirect immunofluorescence and enzyme immunoassay, which is the most sensitive and specific test (7).

Because of the patient did not come back, so we could not perform IFA and MAT test and the definitive diagnosis could not be done. Behind this, there might be dual infection of rickettsia and leptospira in our patient. Moreover, although there were no data about the cross reaction between *Leptospira* spp. and *Rickettsia* spp. in literature, there might be a cross reaction in our case. *Proteus* OX2 antibodies were seen in Mediterranean spotted fever. In our opinion, our patient's rickettsiosis was Mediterranean spotted fever because of Mediterranean spotted fever was endemic in Turkey and *Proteus* OX2 antibodies were positive at 1:2560 titer in Weil-Felix test.

In leptospirosis, doxycycline is recommended for both prophylaxis and mild diseases. Ampicillin and amoxicillin are also recommended in mild disease,

whereas penicillin and ampicillin are indicated for severe disease (2). Doxycycline may be use in treatment of *Rickettsia* spp. infection but, *Rickettsiae* are resistant to beta-lactam antibiotics. The prognosis in spotted fever group of rickettsiosis is largely related to the timeliness of initiation of appropriate therapy (7).

In summary, rickettsial meningitis and leptospiral meningitis should be included in the differential diagnosis of aseptic meningitis in patients exposed to endemic areas, especially when accompanied by renal insufficiency and/or high level of transferases. Clinicians must be aware of leptospiral and rickettsial meningitis because of, sometimes differential diagnosis of leptospiral and rickettsial meningitis couldn't be done in endemic areas.

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