Open Journal of
Clinical & Medical
Case Reports

Volume 3 (2017)
Issue 16

ISSN 2379-1039

Neurological case of Mediterranean spotted fever, Greece

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Abstract

We report a severe case of Mediterranean spotted fever presented with symptoms from the nervous system. PCR was negative in blood, however, PCR on an eschar swab specimen set the diagnosis of infection by *Rickettsia conorii*. The early diagnosis and treatment with doxycycline led to favorable outcome of the disease without sequelae.

Keywords

Mediterranean spotted fever; *rickettsia conorii*; nervous system; Greece

Introduction

Mediterranean spotted fever (MSF) is widely distributed in the Mediterranean countries and it is caused by *Rickettsia conorii* transmitted by the brown dog tick *Rhipicephalus sanguineus*. MSF is usually a benign illness characterized by fever, rash and inoculation black eschar(s) (tache noire) at the site of the tick bite(s). Neurologic involvement is seen mainly in patients with underlying disease or in elderly persons, and it is associated with severe disease with neurological sequelae or fatal outcome [1].

Greece is a Mediterranean country where MSF is endemic, and cases occur usually from May to October. Currently, 4 tick-borne *Rickettsiae* species have been detected in humans in Greece: *R. conorii*, *R. aeschlimannii*, *R. sibirica mongolotimonae*, and *R. slovaca*, while *R. massiliae*, *R. rhipicephali, R. africae, R. monacensis*, and *Candidatus R. barbariae* have been identified only in ticks [2-6]. It is believed that the disease is underdiagnosed, especially in cases without the typical eschar. The number of reported cases accompanied by neurological symptoms is also limited [7,8].

Case Presentation

In June 2015, a 75-year-old male farmer living in a rural area was admitted to the Internal Medicine Department of the Pella Hospital with fever, headache, neck ache, and difficulty on turning the head, progressive paralysis of the lower limbs and decreased consciousness. His medical history included type 2 diabetes mellitus and arterial hypertension. On physical examination, he presented fever (38.1°C) with localized maculopapular rash on the lower limbs. The patient did not report any tick bite; however a 3 mm-diameter eschar was seen on his right lower abdomen. Lymphadenopathy was not present. The neurological examination showed muscle weakness, confusion, Barré sign positive for the upper and lower limbs, and Glasgow coma scale (GCS) score 13. Main laboratory findings were: white blood cells

9,100/μl with 85% neutrophils, hemoglobin 12 g/dl, C-reactive protein 20.2 mg/dl, urea 94 mg/dl, creatinine 1.58 mg/dl, sodium 127 mmol/l, international normalized ratio 1.28, prothrombin time 15 seconds, activated partial thromboplastin time 33.3 seconds, and glucose 335 mg/dl, while platelet and transaminases levels were normal. Lumbar puncture yielded *clear* cerebrospinal fluid (CSF) with normal tension and no cells, glucose 83 mg/dl and protein 55 mg/dl. No abnormal changes were seen in the head computed tomography and the cervical spine and chest radiographies, while the abdominal radiography showed fecal impacted colon and left paracolic gutter level in the right colon. MRI and nerve conduction studies were not performed.

CSF and blood cultures were negative for common pathogens. DNA was extracted from patient's blood and from a swab specimen taken from the eschar on the 5th day after symptoms' onset. Nested PCRs that amplify a 360-bp fragment of the 17 kDa outer membrane antigen gene and a 632-bp fragment of the outer membrane protein A were performed (9, 10). No rickettsial DNA was detected in the blood; however the PCRs from the swab specimen were positive and sequencing of the PCR products showed infection with *R. conorii*. Sequences of both genes were identical to respective ones from *R. conorii* strain Malish 7 (GenBank accession number AE006914). Indirect immunofluorescence assay performed on serum samples taken 5 and 18 days after disease onset, revealed a >4-fold increase in IgM antibodies specific for the spotted fever group rickettsiae (1:64 and 1:512, respectively) (Focus Diagnostics, CA, USA). Low lever cross-reactivity was observed with *R. typhi*.

Empiric treatment was started with doxycycline per os (100 mg/12h), intravenous (IV) ceftriaxone (2gr daily in one dose) and IV acyclovir (500mg daily in 3 doses). Following the laboratory diagnosis of rickettsiosis, ceftriaxone and acyclovir treatment was disrupted. After 4 hospitalization days the fever resolved. The maculopapular rash worsened to petechial, subsiding few days later. The patient improved progressively with recovery of muscle strength; he was discharged after 11 hospitalization days. He continued the treatment with oral doxycycline (100mg/12h) for 8 additional days. On one month-follow-up, the patient reported leg weakness. He progressively recovered and 2.5 months after discharge the recovery was complete without any neurological impairment.

Discussion

The early diagnosis and prompt initiation of doxycycline is crucial for the outcome of MSF, while treatment for at least 15 days has been suggested for cases with neurological manifestations [11]. In our case, the diagnosis of the disease was confirmed by PCR performed on the eschar swab specimen, while the PCR on the blood specimen was negative. Given that antibodies are detectable 7-15 days after the onset of the disease, the PCR from the eschar swab is a valuable early diagnostic tool [12].

R. conorii infects the vascular endothelial cells and stimulates expression of cytokines and pro-coagulant factors resulting in increased vascular permeability. Although the vascular lesions are seen mainly in the skin, many tissue types can be affected and the patient may present symptoms from various systems [13]. Encephalitis is one of the most severe and life-threatening complications of MSF; therefore, the early diagnosis and initiation of therapy is critical for patients' life. Especially since early eighties, MSF appears to be more severe than in the past, and the number of reports on complicated cases, including those with neurological involvement, is increasing [14,16]. The absence of rash in some encephalitis cases caused by *R. conorii* may complicate even further the differential diagnosis [17]. While the history of

a tick bite can help physicians to suspect MSF, in many cases it goes unnoticed. A syndromic approach, taking into account all available clinical and demographic data, combined with surrogated indicators, facilitates the diagnosis and the selection of the laboratory tests to be ordered [18].

In general, MSF presents with many faces and, sometimes, the course of the disease is complicated. Since the early and effective treatment is essential, awareness of physicians is needed to suspect and treat promptly the rickettsial infections presented with any "face".

Acknowledgement

The work was supported by the EU Horizon 2020 research and innovation programme COMPARE (grant agreement No 643476).

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Manuscript Information: Received: June 02, 2017; Accepted: August 07, 2017; Published: August 10, 2017

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Citation: Papa, Sachinidis AG, Vasileiou AM, Kontana A, Anastasiadou A. Neurological case of Mediterranean spotted fever, Greece. Open J Clin Med Case Rep. 2017; 1298.

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