Malignant Mediterranean spotted fever

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Abstract

Mediterranean spotted fever has long been considered as a benign disease, but associated with septic shock and encephalitis, becomes malignant and potentially fatal. We present the case of a 77 year-old man admitted into the emergency room after tick bite in abdominal region and fever 39.6°C. After admission, a maculopapular rash appears with the achievement of palms and soles associated with behavioral changes and adult respiratory distress syndrome. In intensive care CSF examination revealed 6 nuclear elements and a protein level of 94 mg/dL, and electroencephalogram supported the existence of encephalitis. Rickettsia serology by indirect immunofluorescence showed IgG> 1/640 and IgM=1/80. Septic shock, responded to antibiotic therapy and patient was discharged to long term care. This case demonstrates that a benign and common disease suffered a poor outcome owing to the accelerated clinical course with acute onset and rapid deterioration.

Keywords: *Mediterranean spotted fever, septic shock, encephalitis*

Introduction

Mediterranean spotted fever (MSF) is a zoonosis endemic in countries bordering the Mediterranean basin, with summer seasonality [1]. The causative agent *Rickettsia conorii* (*R.conorii*) is transmitted to man by the bite of the brown dog tick, *Rhipicephalus sanguineus*, which was suspected to be the vector. The classic clinical triad is composed of high fever (> 39ºC), maculopapular rash non-pruriginous, typically involvement palmoplantaris but sparing the face and an inoculation eschar at the site of the tick bite. Treatment relies mainly on doxycycline 200 mg/day and duration of treatment should be headed by clinical response, being usually safe to conclude its 24-48 hours after fever ending. The newer macrolides and chloramphenicol may be suitable alternatives.

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In the last decade of the 20th century, there was an increase of malignant form of MSF in Portugal, with a 32.3 % mortality rate in year 1997 [2], in Beja, a southern Portuguese district. Raoult et al. [3] described first severe cases, malignant form, of this apparent benign disease. Its mechanism of infection consists of vascular endothelial invasion by the microorganism and subsequent vasculitis and tissue necrosis. This process can progress with malignant severe systemic involvement and results from a diffusion process of vasculitis, involving various organs leading to multiple organ failure.

Case report

On September 2013, a 77 year-old caucasian men came to the emergency room (ER) with a three-day history of fever (38.5-39.5°C), front-occipital headaches and generalized myalgia, associated with nausea, vomiting, adinamia and asthenia. Five days before the beginning of these symptoms he reported to have been bitten by a tick in abdominal region when it was in his backyard.

He had as a hobby agriculture and past history in 2003 by radical prostatectomy of prostate carcinoma currently medicated with bicalutamide 50 mg / day.

The clinical observation in the ER, the patient were prostrated, blood pressure 112/85 mmHg, heart rate 91 bpm, febrile (39.6°C), normal cardiac and pulmonary auscultation, abdominal diffuse pain without organomegaly, no edemas and a normal neurologic examination. Initial laboratory tests showed the following values: C-reactive protein level 23.49 mg/dl; thrombocytopenia (60,000/µL); leukopenia (3,100/µL); hyponatremia (131mmol/L); serologic study results were negative for Weil-Felix reaction, as well as Leptospirosis, Borrelia, Mycoplasma pneumonia, Chlamydia pneumonia, Legionella pneumophila, Brucellosis and Coxiella burneti. Diagnostic imaging was performed with abdominal computed tomographic scan and lung X-ray, which were normal. It was admitted in the acute medical assessment unit with a diagnosis of the systemic inflammatory response syndrome unfocused, after blood and urine cultures started ceftriaxone 2 gr IV q24.

On day 1 appears maculopapular rash with the accomplishment of the palms and soles of the feet. Remained ceftriaxone and doxycycline 200 mg IV q12 was associated. On day 2, the patient develops mental confusion and disorientation, high fever (39ºC), hemodynamic instability (blood pressure 94/51 mmHg, heart rate 109 bpm) associated with ARDS (adult respiratory distress syndrome - Figure 1). The patient was transferred to the intensive care unit (ICU) in which arterial blood gas revealed respiratory acidemia when breathing 50% oxygen (pH 7.34, pCO2 22 mmHg, pO2 66 mmHg, HCO3 19.2 mmol/L), and with hyperlactacidemia (lactic acid 2.8 mmol/L). Lab testing showed severe thrombocytopenia (42,000/µL), an acute kidney injury (creatinine 2.49 mg/dl; blood urea nitrogen 110 mg/dl), and abnormal liver tests (total bilirubin of 2.48 mg/dL; alanine transaminase [ALT]: 165 IU/L; aspartate transaminase [AST]: 352 IU/L), a prothrombin rate of 42% and lactate dehydrogenase levels (790 IU/L) were ordered with multiple organ dysfunction. Serologic evaluation was negative for HIV, T. pallidum and was ruled out for hepatitis. Blood culture and urine culture were ordered. The patient was stabilized by mechanical ventilation, fluid resuscitation; inotropic agents and imipenem with dose adjustment for renal impairment were administered.

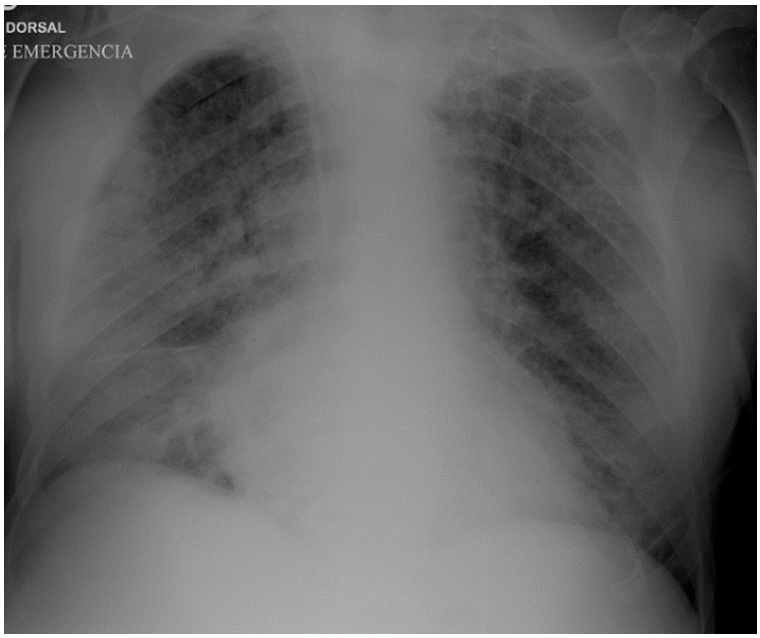

Fig.1. Chest radiography reveals bilateral alveolar infiltrates

In ICU, keeping impaired consciousness and observations of facial myoclonus, without sedation, a traumatic lumbar puncture was done. Cerebrospinal fluid (CSF) revealed 660/uL erythrocytes, 6/uL cells and protein 94 mg/dL. Direct examination, cultures and rickettsial DNA in CSF were all negative. A brain computed tomography showed no acute structural damage and electroencephalogram (EEG) was compatible with encephalitis (Figure 2). Doxycycline treatment was maintained for 15 days. After 10 days of treatment, the fever and rash have disappeared. The acute kidney injury also resolved. All blood and urine cultures were negative. No other source of infection was found. However, he continued to require mechanical ventilation.

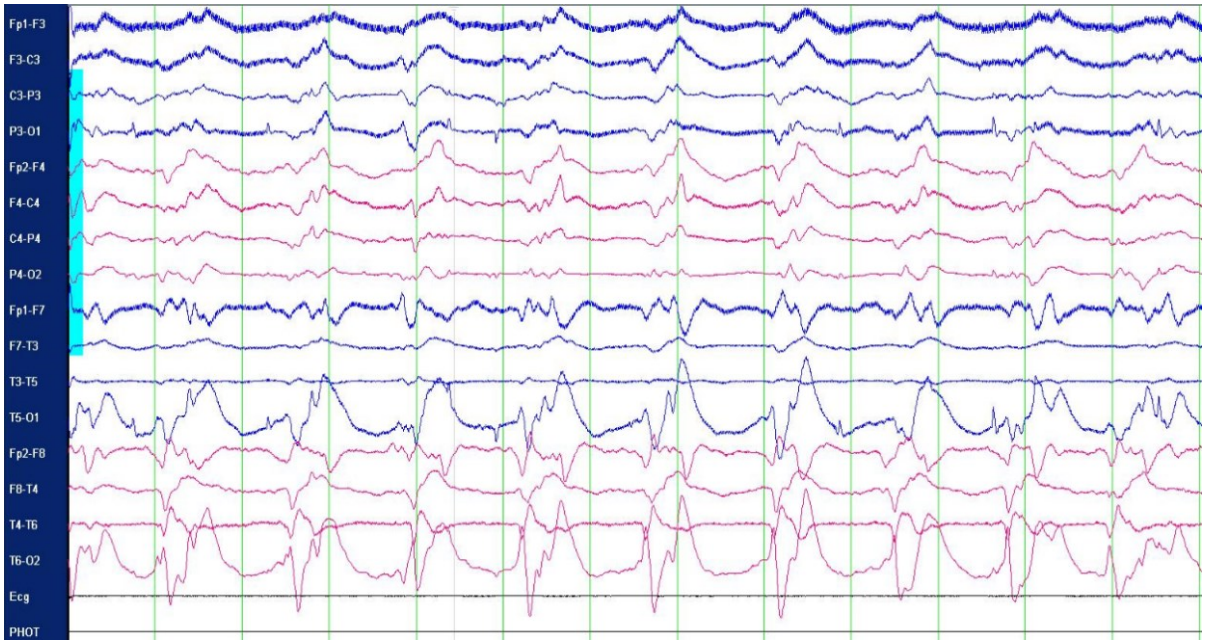

Fig.2. Almost, continuous abrupt wave - slow wave, with large abrupt wave temporo-occipital right and generalized surges of abrupt waves with intervals of one second.

On the 17th hospital day, he was transferred to the internal medicine department for continuing care, still suffering from tetraparesis, in sequence of prolonged mechanical ventilation. In this general medical ward is requested serology for *R. conorii* by immunofluorescence assay (IFA) was positive, with IgM = 80 and IgG > 1/640. Brain magnetic resonance imaging (MRI) showed diffuse brain injury shown by the extensive alteration of cortical signal and supratentorial white matter of temporal predominance, insular and occipital-parietal bilaterally and the left thalamus, characterized by a signal hyperintensity in T2 and FLAIR, with restricted areas to the diffusion of water (Figure 3).

The patient starts physical medicine and rehabilitation, watching to a gradual improvement and was discharged for a long term care, with some recovery of motor functions and improvement of consciousness.

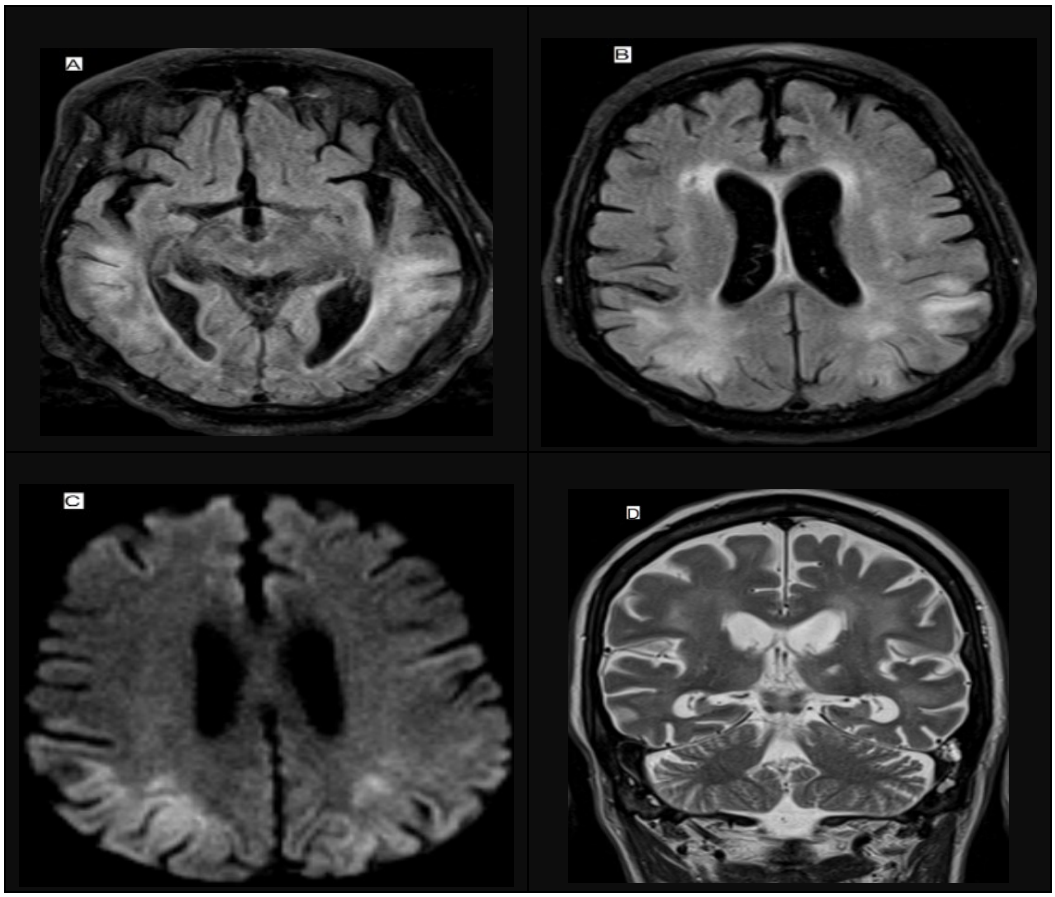

Fig.3. Axial FLAIR - hyperintense white matter bilateral temporo-occipital (A). Bilateral parietal (B). Restriction diffusion sequence to the diffusion of water and parietal cortical-subcortical occipital bilaterally (C). Coronal T2 - focused image of hyperintense signal on T2 in the left thalamus sequence (D).

Discussions

Although most cases of MSF are mild, severe and fatal events are likewise considered in the literature. These patterns result from a diffuse vasculitis process, involving various organs, which results from the proliferation of Rickettsia in vascular endothelial cells. Identified risk factors are: advanced age, immunosuppression, diabetes, cardiac insufficiency, chronic alcoholism, respiratory insufficiency, G6PD deficiency, delay in treatment and inadequate antibiotic therapy [3].

This disease, endemic in Portugal, has a summer incidence, as we have found out in this example. The clinical spectrum of the disease is quite variable, from asymptomatic to fulminant forms, but almost only diagnosed after the typical purpuric rash appearance in a patient with a history of tick bites. In our case was about five days before the onset of symptoms, that the patient had been cultivating the land at his backyard, and reported to have been bitten by a tick in the abdominal region. To complete the classical triad characterized by fever, rash (with palm and sole distribution) the inoculation scar ("tache noire") is not found. The patient had many of the features typical of MSF, including headache, myalgia, rash, renal impairment and thrombocytopenia. The presence of hypotension, prostration, altered mental status, lactate 2.8 mmol/L, thrombocytopenia, low prothrombin rate, high levels of total bilirubin, an acute kidney injury and with Pao2/Fio2 < 250 in the absence of pneumonia as infection source, this clinical condition was compatible with severe sepsis. All blood and urine cultures of patient were negative and no source of infection was found.

A case of septic shock unfocused of a 56 year-old woman after a holiday in Turkey was published in 2006 [4]. She stayed 8 days in the intensive care unit and 7 days on a general medical ward. She was discharged home without any definite diagnosis for the septic event. Eight weeks after discharge, serological results were received which showed immunoglobulin M against the Rickettsia spotted-fever group, consistent with a recent spotted-fever infection.

Another case report of 45 year-old woman [5] with shock and ARDS was admitted to ICU. All cultures were negative, and only in the tenth day a physical examination disclosed a black scar under the hair on the head. Blood was collected for serologic and a positive Weil-Felix reaction and complement fixation antibodies for *R. conorii* were found.

The pathological consequences in human infections from *R. conorii* [6, 7], implicate disseminated infection of the endothelial cell of various organ systems, leading to vascular damage, inflammation and permeability changes. *R. conorii* has been demonstrated in the pulmonary blood vessels, and pulmonary lesions including pulmonary edema and vasculitis have been described in fatal cases. Noncardiogenic pulmonary edema results from rickettsial infection of the pulmonary microcirculation, vascular injury, and consequently increased vascular permeability.

In our patient, the findings from the second lung X-ray, the bilateral alveolar interstitial infiltrates and the severe hypoxemia with PaO2/FIO2 no higher than 200 were compatible with ARDS. Although pulmonary involvement has been often described in severe human RC infection, is a rare cause of ARDS.

In that respect, is no reliable test to diagnose the infection in its early stages and the diagnosis is usually clinical.

The most accurate method for the diagnosis of *R. conorii* infection is the identification of the agent, either by PCR, cell culture or by immunostaining in tissue specimens. However, the detection of antibody to *R. conorii* by immunofluorescence (IFA) remains the best-recognized and most available laboratory method to diagnose Mediterranean spotted fever. So, the serological tests are the most specific, but apart from not always available, the result is not immediate. Measurement of IgG and/or IgM to *R. conorii* is a useful tool for diagnosing the infection (acute disease) and estimating the time since exposure. IgM reactivity in the absence of IgG reactivity may represent false positive reaction.

The prevalence of IgG-antibodies reactive with an Israeli strain of *R. conorii*, was examined in humans and dogs from two rural villages in Israel where the disease has been reported in humans. Sixty-nine of 85 (81%) canine sera and 14 of 136 (10%) of human sera had anti-*R. conorii* antibodies. No direct association could be made between seropositivity of people and ownership of a seropositive dog. This study indicates that exposure to spotted fever group rickettsiae was highly prevalent among dogs compared with humans in the two villages examined, probably reflecting a greater exposure rate of canines to the tick vector. These results support a previous suggestion that canine serology could be a sensitive indicator of the presence and magnitude of human exposure to *R. conorii*.

Interestingly, a relatively high prevalence of anti- rickettsiae antibodies (IgG - positive at 1:100 titers) was found, whereas only two human clinical cases had been diagnosed. The presence of antibodies without apparent clinical manifestations suggests that most *R. conorii* exposures in this study were asymptomatic or accompanied by mild or non-specific symptoms that were not associated with MSF at the time of occurrence. IgG antibodies persist for several years post-MSF in humans. The presence of anti- *R. conorii* IgM in 13 of the 14 seropositive people in this study suggests recent exposure to the rickettsia. [8]

However, the diagnosis of *R. conorii* infection should be confirmed when serum samples obtained from patients with acute infection contained IgM antibodies at a titer of ≥ 32 and/or IgG titer of ≥ 128 or there was a 4-fold increase in titer between serum samples from patients with acute infection and samples from convalescent patients. This cutoff for a positive result for *R. conorii* infection was established by the Portuguese National

Institute of Health [9] on the basis of previous studies in the Portuguese population and previous studies of Portugal as a country where MSF is endemic. Molecular methods based on polymerase chain reaction (PCR) have enabled the development of sensitive, specific and rapid tools to detect Rickettsia in clinical samples [10], but the quick elimination following the treatment with doxycycline is intrinsic difficulties in using PCR assays for the diagnosis of rickettsial diseases. Thus, diagnosis is made on the basis of clinical features which are generally nonspecific and easily confused with other conditions.

Currently, at the *Unite des Rickettsies* in Marseilles, IgG titres ≥ 128 and/or IgM titres ≥ 64 are considered indicative of infection by *R. conorii* in suspected cases of MSF. At the same [11], case definitions and diagnostic scores have been established for MSF and whose serological criteria are: single serum and IgG > 1/128 [score 5] or single serum and IgG > 1/128 and IgM > 1/64 [score 10] (our case) or fourfold increase in two sera obtained within a 2-week interval [score 20].

The clinical case herein described, it was held on the 1st day Weil-Felix which was negative, and the serological tests by immunofluorescence assay (IFA) were realized in 19º day of illness, which were IgG> 1/640 and IgM=1/80.

If we use the European Guidelines for the diagnosis of MSF [11], based on epidemiologic, clinical, and laboratory data, the positive diagnosis is established when the overall mark is larger than or equal to 25 (Table 1), and in our case the score was 29.

Table 1. Diagnostic criteria for Mediterranean spotted fever caused by *Rickettsia conorii* [11]

		Score
Criteria		
Epidemiological	Stay in endemic area	2
	Occurrence in May–October	2
	Contact (certain or possible) with dog ticks	2
Clinical	Fever > 39º C	5
	Eschar	5
	Maculopapular or purpuric rash	5
	Two of the above criteria	3
	All three of the above criteria	5
Laboratory	Platelets < 150 G/L	1
	SGOT or SGPT > 50 U/L	1
Bacteriological	Blood culture positive for Rickettsia conorii	25
	Detection of Rickettsia conorii in a skin biopsy	25
Serological	Single serum and IgG > 1/128	5
	Single serum and IgG > 1/128 and IgM > 1/64	10
	Fourfold increase in two sera obtained within a 2-week interval	20

Even if, our patient reported to have been bitten by a tick and has had rash characteristic, a variety of conditions must be counted in the differential diagnosis of this case who was affiliated with adult respiratory distress syndrome and encephalitis. Features of some disorders that are included in the differential diagnosis are shown in the Tables 2 and 3.

Table 2. Clinical conditions associated with development of Acute Respiratory Distress [12]

Direct lung injury	Indirect lung injury
Pneumonia	Sepsis
Aspiration of gastric contents	Severe trauma
Inhalation injury	Acute pancreatitis
Near drowning	Cardiopulmonary bypass
Pulmonary contusion	Massive transfusions
Fat embolism	Drug overdose
Reperfusion pulmonary edema	

Table 3. Etiologic agents of encephalitis based on epidemiology and clinical findings [13]

Epidemiology		Clinical presentation	
Risk factor	**Possible infectious agent(s)**	**General findings**	**Possible infectious agent(s)**
Elderly persons	Eastern equine encephalitis virus	Rash	Varicella virus zoster
	St. Louis encephalitis virus		Human herpesvirus
	West Nile virus		West Nile virus
	Sporadic CJD		Rubella virus
	L. monocytogenes		HIV
Camping	All agents transmitted by mosquitoes and ticks		Rickettsia rickettsii
Summer			Mycoplasma pneumoniae
	Enteroviruses		Borrelia burgdorferi
Europe	West Nile virus		T. pallidum
	Tick borne encephalitis virus		Ehrlichia chaffeensis
	A. Phagocytophilum		A.Phagocytophilum phagocytophilum
	B. burgdorferi		Venezuelan encephalitis
Ticks	Tickborne encephalitis virus	Respiratory Tract Findings	Nipah virus
	Powassan virus		Hendra virus
	Rickettsia rickettsii		Influenza virus
	Ehrlichia chaffeensis		M. pneumoniae
	A. Phagocytophilum		C. burnetii
	Coxiella burnetii		M. tuberculosis
	B. burgdorferi		Histoplasma capsulatum
		Hepatitis	Coxiella burnetii

Neurological involvement has been reported in 28% of patients [14] and constitutes a negative predictive factor for the effect of the disease. Neurological complications of MSF include clinical pictures of meningitis and meningoencephalitis. Our patient received a clinical presentation of meningoencephalitis, based in impaired consciousness and observations of facial myoclonus, and the cerebrospinal fluid (CSF) revealed 660/uL erythrocytes, 6/uL cells and protein 94 mg/dL. Direct examination, cultures

and rickettsial DNA in CSF were all negative. The presence of erythrocytes was done with a traumatic lumbar puncture and TAC in ICU and RMN in medical ward do not reveal signs of hemorrhage. The tetraparesis mentioned is in sequence of prolonged mechanical ventilation. He had been 17 days in ICU and ventilator 16 days. In association, the EEG had generalized irregular slow waves suggestive of encephalitis and the MRI showed multiple, white matter lesions hyperintense on T2-weighted sequences and FLAIR, with restricted areas to the diffusion of water.

In a case report of 66 year-old man and reviewed the medical literature [15], the man has presented slurred speech at ER and the computed tomography (CT) scan of the head, revealed no abnormalities. The CSF sampling exhibited 2400/uL erythrocytes, 2/uL cells and protein 55 mg/dL and 95 mg/ dl glucose. The magnetic resonance imaging (MRI) showed increased subcortical white matter signal abnormalities on diffusion, flair and T2-weighted sequences in the frontal, parietal and occipital lobes. In that search, they found 29 cases of MSF diagnosed concomitantly with encephalitis or meningoencephalitis and only six case reports from literature met convincingly their criteria for encephalitis, illustrating the major involvement of the central nervous system. All patients presented with severe disease with several complications, along with fever and rash. One patient had no eschar. The neurological manifestations were dominated by the altered state of consciousness. CSF was analyzed in five patients and showed minor abnormalities. Two patients showed erythrocytes in their CSF, a finding that also may be due to a traumatic lumbar puncture. A brain CT scan was performed in five patients, showing abnormalities for two of them. MRI of the brain was performed in two patients; in both patients the MRI showed diffuse alterations in the cerebral lobes, cerebellar peduncles and corpus callosum. Among the four patients who survived only one was without sequelae. Sequelae were severe in the remaining three, despite appropriate treatment.

It is apparent that the breakup of the clinical syndromes of aseptic meningitis and encephalitis is not always comfortable. According to L. Aliaga et al [15], must be considered encephalitis caused by *R. conorii* to be present when a patient met the following criteria: a diagnosis of MSF according to standard criteria, acute symptoms of brain dysfunction, and inflammatory brain lesions evidenced by necropsy or suggested by neuroimaging techniques.

Complications and death have been associated with advanced age, debilitating underlying conditions and delay in appropriate treatment [16].

Conclusion

Severe cases of Mediterranean spotted fever can present with atypical signs. The eventual patient instability can lead to the consideration of a different diagnosis, usually of infectious origin, until the confirmation being made by serology.

To our knowledge, this is the first case of a reversible shock septic and encephalitis in a patient with rickettsial infection. This case emphasizes the importance of considering Mediterranean spotted fever in the differential diagnosis of a patient with fever and rash, especially in the elderly which living in endemic areas.

The finding from the present clinical case must support the recommendations that older adult patients in the emergency room with sudden high fever, and important comorbidities may benefit from routine screening for brown bitten tick.

References

1. Parola P, Socolovschi C, Raoult D. Deciphering the relationships between Rickettsia conorii and Rhipicephalus sanguineus in the ecology and epidemiology of Mediterranean spotted fever. *Ann N Y Acad Sci* 2009; 1166:49-54.
2. De Sousa R, Nobrega SD, Bacellar F.

Mediterranean spotted fever in Portugal: risk factors for fatal outcome in 105 hospitalized patients. *Ann N Y Acad Sci* 2003; 990:285–294.

3. Rovery C, Raoult D. Mediterranean Spotted Fever. *Infect Dis Clin N Am* 2008; 22:515-530.
4. E Chipp and S Digby. Rickettsia: an unusual cause of sepsis in the emergency department. *Emerg Med J* 2006; 23:e60.
5. Angel Lopez Rodriguez; Vicente Jerez; Ann Garcia Lombardo. ARDS associated with Boutonneuse Fever. *Chest* 1989; 95:924-925.
6. Walker DH, Gear JHS. Correlation of the distribution of Rickettsia conorii, microscopic lesions, and clinical features in South African tick-bite fever. *Am J Trop Med Hyg* 1985; 34:361-371
7. Walker DH, Herrero-Herrero JI, Ruiz-Beltran R. The pathology of fatal Mediterranean spotted fever. *Am J Clin Pathol* 1987; 87:669-672.
8. Shimon Harrus, Yael Lior, Moshe Ephros, et al. Rickettsia conorii in Humans and Dogs: A Seroepidemiologic Survey of Two Rural Villages in Israel. *Am J Trop Med Hyg* 2007; 77:133–135.
9. Sousa R, França A, Nóbrega SD. Host and microbe-related risk factors for and pathophysiology of fatal Rickettsia conorii infection in Portuguese patients. *J Infect Dis* 2008; 198:576–585.
10. Santibánez S, Portillo A, Santibánez P. Usefulness of rickettsial PCR assays for the molecular diagnosis of human Rickettsioses. *Enferm Infecc Microbiol Clin.* 2013; 31:283–288.
11. Brouqui P, Bacellar F, Baranton G, et al. Members of ESCAR (ESCMID Study Group on Coxiella, Anaplasma, Rickettsia and Bartonella) and the European Network for Surveillance of Tick-Borne Diseases. Guidelines for the diagnosis of tick-borne bacterial diseases in Europe. *Clin Microbiol Infect* 2004; 10:1108–32.
12. Ware LB, Matthay MA. The acute respiratory distress syndrome. *N Engl J Med* 2000; 342:1334-1349.
13. Tunkel AR, Glaser CA, Bloch KC, et al. The Management of Encephalitis: Clinical Practice Guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 2008; 47:303–327.
14. Alioua Z, Bourazza A, Lamsyah H, et al. Neurological feature of Mediterranean spotted fever: a study of four cases. *Rev Med Interne* 2003; 24:824–829.
15. Aliaga L, Sánchez-Blázquez P, Rodrı´guez-Granger J, Sampedro A, Orozco M, Pastor J. Mediterranean spotted fever with encephalitis. *J Med Microbiology* 2009; 58:521–525.
16. Botelho-Nevers E, Raoult D. Host, pathogen and treatment-related prognostic factors in rickettsioses. *Eur J Clin Microbiol Infect Dis* 2011; 10:1139-1150.