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Multiple organ failure as onset of Mediterranean spotted fever: a review based on a case

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ABSTRACT

Mediterranean spotted fever (MSF) is an infectious disease endemic in the southern regions of Italy, with an incidence of about 400 cases/year. The bacteria responsible of the disease is *Rickettsia conorii*, transmitted to humans by *Rhipicephalus sanguineus*, the common dog tick. The infection usually manifests with a characteristic symptomatologic triad: fever, exanthema and the so called *tache noire*, which is the typical eschar at the site of the tick bite. Immunoglobulin M (IgM) and IgG enzyme-linked immunosorbent assay and the gold standard micro-immunofluorescent assay, allow serological diagnosis. We report the case of a man suffering from MSF, whose atypical presentation and false-negative diagnostic tests delayed consistently diagnosis and therapy. Afterwards we review the literature about this topic.

Introduction

Rickettsia conorii infection is a common infection in the southern regions of Italy and in particular in Sicily with nearly 400 cases of Mediterranean spotted fever (MSF) reported every year, mainly from June to September.[1] It accounts among the arthropod borne diseases: the responsible of transmission to humans is *Rhipicephalus sanguineus*, the common dog tick.[2] The infection usually manifests with a characteristic symptomatologic triad: fever, exanthema and the so called *tache noire*, which is the typical eschar at the site of the tick bite. Its diagnosis is quite simple, when suspected, thanks to the modern laboratory techniques, which have outdated the Weil-Felix agglutination test, as immunoglobulin M (IgM) and IgG enzyme-linked immunosorbent assay (ELISA) and micro-immunofluorescent assay (IFA).[3-8] About 6% of patients develop severe forms of the disease with a mortality rate reported up to 2.5%; the subjects who are at the highest risk are adults with one or more of the following conditions: cardiac diseases, end stage kidney disease, chronic alcoholism, diabetes and glucose-6-phosphate dehydrogenase deficiency.[2]

In 1992 the American College of Chest Physicians and the Society of Critical Care Medicine defined the multiple organ dysfunction syndrome/multiple organ failure (MODS/MOF) as *presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention*.[9] Representing a systemic condition that could be associated with several diseases, it is not possible to define specific epidemiological data about it, but MODS/MOF has been reported to be a major cause of mortality in acute respiratory distress syndrome, systemic inflammatory response syndrome (SIRS), trauma, sepsis and several other critical illnesses.[9-13]

To our knowledge there are only few cases of MSF reported to be complicated by MODS/MOF. Here we report the case of a 59-year-old male affected by MSF whose onset was characterized by MODS/MOF, using

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it to critically revise the international literature, focusing on the possible diagnostic and therapeutic delays due to the atypical presentations and the use of non-specific and non-sensible laboratory tools.

Case presentation

A 59-year-old deaf and dumb man came to our attention due to the onset, about 7 days before admittance, of fever, characterized by peaks of 39°C, and shaking chills, profuse sweating, headache, arthromyalgia, and marked asthenia. For this symptomatology, after a consultant with general care practitioner, he performed home therapy with amoxicillin and acetaminophen without benefit. He reported a past medical history with chronic cerebrovascular disease, in treatment with acetylsalicylic acid (100 mg/day), and celiac disease (CD), treated with gluten-free diet. At physical examination the patient proved alert, cooperative, eupneic, tachycardic (105 bpm) and with normal blood pressure; no abnormalities were found at examination of the main organs, excluding tachycardia and mild hepatosplenomegaly. Biohumoral exams at admission showed leukocytosis with neutrophilia and thrombocytopenia, together with elevated aminotransferase, direct bilirubinemia, lactic dehydrogenase (LDH), serum creatinine levels, and C reactive protein (CRP) (Table 1). Arterial blood gas analysis showed an acute lung failure with respiratory alkalosis and concomitant metabolic

Table 1. Hematochemical analysis at admission.

Hematochemical parameter	Value	Reference values
Red blood cell count	3.65×10^{12}/L	$4.4\text{-}5.7\times10^{12}$/L
Hemoglobin	11.6 g/dL	13-17 g/dL
Hematocrit	33.6%	40-52%
Mean corpuscular volume	92.1 fL	82-96 fL
Mean corpuscular hemoglobin	31.9 pg	27.0-32.0 pg
White blood cell count	12.4×10^{3}/L	$4\text{-}10\times10^{3}$/L
- Neutrophils	10.6×10^{3}/L (85.4%)	$2.0\text{-}7.0\times10^{3}$/L (55-70%)
- Lymphocytes	0.8×10^{3}/L (6.6%)	$1\text{-}4\times10^{3}$/L (25-35%)
- Monocytes	0.61×10^{3}/L (5.1%)	$0.2\text{-}0.8\times10^{3}$/L (1-8%)
- Eosinophils	0.20×10^{3}/L (1.6%)	$0.1\text{-}0.5\times10^{3}$/L (1-4%)
- Basophils	0.15×10^{3}/L (1.3%)	$0\text{-}0.2\times10^{3}$/L (0-1%)
Platelets	36×10^{3}/L	$150\text{-}400\times10^{3}$/L
C-reactive protein	343.2 mg/L	0-5 mg/L
Erythrocytes sedimentation rate (1st h)	24 mm	1-10 mm
Aspartate aminotransferase	354 U/L	10-40 U/L
Alanine aminotransferase	129 U/L	9-41 U/L
Alkaline phosphatase	134 U/L	40-129 U/L
Gamma glutamyl transferase	161 U/L	8-61 U/L
Total bilirubin	5.97 mg/dL	0.2-1.2 mg/dL
Direct bilirubin	4.16 mg/dL	0-0.3 mg/dL
Lactic dehydrogenase	1245 U/L	240-480 U/L
Urea	144 mg/dL	10-50 mg/dL
Creatinine	2.51 mg/dL	0.67-1.17 mg/dL
Serum sodium	137 mEq/L	132-150 mEq/L
Serum potassium	3.7 mEq/L	3.8-5.5 mEq/L
Uricemia	11.5 mg/dL	3.5-7 mg/dL
Serum iron	21 µg/dL	59-158 µg/dL
Ferritin	4692 mg/dL	30-400 ng/mL
Prothrombin time	76%	70-120%
International normalized ratio	1.13	0.8-1.2
Activated partial thromboplastin time	20 s	15-30 s
Fibrinogen	113 mg/dL	150-450 mg/dL
D dimer	21.4 mg/L	0-0.5 mg/L
Brain natriuretic peptide	13,006 pg/mL	<100 pg/mL

acidosis (pH 7.47, pCO_2 25.5 mmHg, pO_2 49.4 mmHg, HCO_3 18.5 mmol/L, lactate 18.6 mg/dL). The computerized tomography (CT) without medium contrast showed pulmonary parenchymal consolidation with areas of atelectasis and bilateral basal minimal pleural. In the first hours after admission, the clinical course was characterized by worsening of respiratory failure and respiratory alkalosis (pH 7.51) and increase in lactate (22.6 mg/dL). At the same time, he showed a progressive reduction in urine output (<0.5 mL/kg/h), as acute kidney failure, and consciousness impairment (Glasgow come scale 5). In view of the suspected prerenal origin of kidney failure, hydrating therapy was practiced with saline infusion rate of 62.5 mL/h. After an initial benefit, with increase in diuresis, however, the clinical framework was further aggravated by the onset of an acute pulmonary edema, with normal contractile left ventricular function (left ventricular ejection fraction 50% at transthoracic echocardiography) and increase in brain natriuretic peptide (13,006 pg/mL, reference values <100 pg/mL) for which the patient initially underwent diuretic therapy with furosemide intravenously (i.v.) and then a dialysis session. The patient was stabilized within the first 48 h after admission and its consciousness improved as well. Then he underwent thoraco-abdominal CT with and without contrast, which proved basal thickening of the right lung, ground-glass areas in the upper and lower lobes, confirmed bilateral pleural effusions, multiple area of pulmonary atelectasis, ground-glass framework, marked splenomegaly (17 cm) and several enlarged abdominal lymph nodes. Considering CT framework, fever with leukocytosis and evidence of active inflammatory status, the patient was diagnosed as suffering from SIRS, complicated by MODS/MOF, according to the criteria of American College of Chest Physicians and the Society of Critical Care Medicine,[9] and i.v. broad-spectrum antibiotics (association of carbapenems and macrolides) together with corticosteroid i.v. (prednisone 125 mg *bis in die*) were stared. Despite therapy, the clinical conditions remain critical, fever persisted high (38-39°C) and white blood cell count, as the CRP, did not show any improvement. Several blood cultures were performed all proving negative for bacteria and fungi. In the suspect of endocarditis, transthoracic echocardiography was repeated but the only evidence was the already known depression of the left ventricular contractile function (left ventricular ejection fraction 60%). To exclude other sources of infectious diseases, urine cultures, as well as serologic determinations, were obtained. These included serologic testing for major and minor hepatitis-causing liver viruses (hepatitis A/B/C viruses, cytomegalovirus, and Epstein-Barr virus), and for *Chlamydia* spp., *Mycoplasma* spp., *Rickettsia* spp. (Weil-Felix agglutination test), *Salmonella* spp., *Brucella* spp., and antistreptolysin titers and streptozyme. Quantitative DNA search to human herpes virus 6 and 8 was also inquired, proving negative. Diagnostic tests for autoimmune diseases (most common autoantibodies, such as antinuclear antibody, extractable nuclear antigen, anti-mitochondrial antibody, anti-smooth muscle antibody, anti-liver kidney microsomes, and anti-neutrophil cytoplasmic antibody), were uniformly negative. Therefore, the persistent low clinical condition, the leukocytosis with neutrophilia, the high values of LDH, the increase in inflammatory markers, and, finally, the CT framework of splenomegaly associated with the increase in volume of the main abdominal lymph node stations, suggested us the diagnostic hypothesis of abdominal lymphoma, possibly of intestinal origin given the known history of CD. Thus, a hematologic consult, with examination of the peripheral blood smear, were required and confirmed leukocytosis with neutrophilia in the absence of marked abnormalities of the red and/or white cells. The seventh day after admission to our Department (14th day after symptoms onset) physical examination showed the appearance of roseoliform rash, with erythematous macular lesions spread to abdomen, as rickettsiosis. Physicians carefully looked for the *tache noir* lesion in the typical areas (nape, neck, armpits, and groin) but this produced no result. This objective finding was in contrast with the evidence of the already performed Weil-Felix agglutination test, which proved negative; thus we repeated the Weil-Felix agglutination test but at the same time we asked for a more sensible and specific test. IFA for IgM proved positive (titer >1/160 for *R. conorii*), and Weil-Felix agglutination test proved positive. Therefore, we started therapy with doxycycline (100 mg *per os, bis in die*) and ciprofloxacin (500 mg *per os, bis in die*) that led to a sudden improvement of the clinical conditions and laboratory results (Table 2) which allowed us to discharge the patient at the thirteenth day after admission. Of notice is the lack of any referred exposure to the arthropod, which was confirmed by the patient and his relatives when inquired, both before and after the diagnosis.

Methods of research

Literature search performed by the PubMed database, using the keywords *rickettsia*, *Mediterranean spotted fever*, *multiple organ failure* and *multiple organ dysfunction syndrome* produced only 7 results.[14-20] Of them, 1 was discharged because not inherent to our search,[19] 3 addressed cases of MOF in Japanese spotted fever caused by *Rickettsia japonica*,[14-16] 1 addressed MOF due to scrub typhus caused by *Rickettsia tsutsugamushi* infection,[18] 1 reported the case of a MSF with MOF,[20] and finally 1 addressed abnormal presentation of *R. conorii* infection in a Turkish European Region.[17]

Discussion

MSF atypical presentation characterized by MODS/MOF is considered as a rare condition. Devriendt *et al.* reported the case of a 77-year-old man who developed acute aqueous diarrhea and hyperpyrexia treated with sulfadiazine, followed 2 days later by the appearance of an erythematous, non-pruriginous rash. Ten days after the symptoms onset the patient developed coagulopathy and mild hepatitis. The authors report they performed Weil-Felix agglutination test but, as in our case, it was negative. The patient was transferred to intensive care unit due to the worsening of clinical condition: acute kidney failure with metabolic acidosis, intravascular disseminate coagulopathy, and acute lung failure which forced mechanical ventilation. The persistence of cutaneous rash urged the physician to perform skin biopsy (reported normal) and to repeat Weil-Felix agglutination test which proved again negative. Nevertheless, the authors demanded IFA for *R. conorii*, which proved positive (>1/280). The patient underwent therapy with doxycycline, with a prompt improvement of clinical condition. Of note, despite several similarities between our case and Devriendt's one, an important difference is the late onset of the cutaneous rash in our patient, which considerably re-

Table 2. Hematochemical analysis at discharge.

Ematochemical parameter	Value	Reference values
Red blood cell count	3.60×10^{12}/L	$4.4\text{-}5.7\times10^{12}$/L
Hemoglobin	11.6 g/dL	13-17 g/dL
Hematocrit	34.7%	40-52%
Mean corpuscular volume	96.0 fL	82-96 fL
Mean corpuscular hemoglobin	32.1 pg	27.0-32.0 pg
White blood cell count	6.3×10^{3}/L	$4\text{-}10\times10^{3}$/L
- Neutrophils	4.21×10^{3}/L (66.7%)	$2.0\text{-}7.0\times10^{3}$/L (55-70%)
- Lymphocytes	1.51×10^{3}/L (24.0%)	$1\text{-}4\times10^{3}$/L (25-35%)
- Monocytes	0.45×10^{3}/L (7.2%)	$0.2\text{-}0.8\times10^{3}$/L (1-8%)
- Eosinophils	0.11×10^{3}/L (1.7%)	$0.1\text{-}0.5\times10^{3}$/L (1-4%)
- Basophils	0.03×10^{3}/L (0.4%)	$0\text{-}0.2\times10^{3}$/L (0-1%)
Platelets	325×10^{3}/L	$150\text{-}400\times10^{3}$/L
C-reactive protein	3.20 mg/L	0-5 mg/L
Erythrocytes sedimentation rate (1^{st} h)	4 mm	1-10 mm
Aspartate aminotransferase	42 U/L	10-40 U/L
Alanine aminotransferase	70 U/L	9-41 U/L
Alkaline phosphatase	66 U/L	40-129 U/L
Gamma glutamyl transferase	50 U/L	8-61 U/L
Total bilirubin	0.9 mg/dL	0.2-1.2 mg/dL
Direct bilirubin	0.2 mg/dL	0-0.3 mg/dL
Lactic dehydrogenase	490 U/L	240-480 U/L
Urea	55 mg/dL	10-50 mg/dL
Creatinine	0.9 mg/dL	0.67-1.17 mg/dL
Serum sodium	140 mEq/L	132-150 mEq/L
Serum potassium	4.2 mEq/L	3.8-5.5 mEq/L
Uricemia	6.5 mg/dL	3.5-7 mg/dL
Serum iron	60 µg/dL	59-158 µg/dL
Ferritin	382 mg/dL	30-400 ng/mL
Prothrombin time	85%	70-120%
International normalized ratio	1.01	0.8-1.2
Activated partial thromboplastin time	22 s	15-30 s
Fibrinogen	289 mg/dL	150-450 mg/dL
D dimer	0.03 mg/L	0-0.5 mg/L
Brain natriuretic peptide	210 pg/mL	<100 pg/mL

tarded our diagnostic process. In addition, our patient was considerably younger (59 *vs* 77 years) and he was not treated with sulfadiazine, a well note drug reported as exacerbating rickettsiosis.[20]

Kuloglu *et al.* performed a prospective evaluation of 11 patients (4 males and 7 females) admitted due to *R. conorii* infection in a 3th level hospital in European Turkey. The authors pointed-out that all patients had high fever, 91% had maculopapular rash, 73% had rash on the palms or on the soles, 45% patients had a unique eschar and 18% had double eschars. Interesting, considering the small number of patients, 2 presented with MOF and one of them died.[17]

In our case, it is important to focus on 2 key points: i) the atypical presentation of the disease; ii) the diagnostic mismatch between Weil-Felix agglutination test and ELISA/IFA.

MSF usually presents with continuous-remitting fever, severe headache, arthromyalgia, maculopapular rash, appearing in 3rd-5th day and spreading to the whole body (including palms or the soles), and, in 40-60% of cases, eschar in the site of inoculation.[2,21] An epidemiological analysis performed in Sicily over 525 patients admitted to the Caltagirone hospital with the diagnosis of MSF showed that 67 (12.7%) had a prevalent organ involvement (Table 3).[22] Noteworthy, only 9 patients had an extremely serious clinical course which caused the *exitus* in all the cases. None of these severe cases was however diagnosed with MOF, especially as onset of clinical framework. The authors concluded that *exitus* occurred in elderly subjects with pre-existing chronic diseases (diabetes mellitus, ischemic heart disease and chronic obstructive pulmonary disease), in healthy young for delay in diagnosis and therapy, and in subjects with massive pulmonary embolism.[22] Similar data have been previously reported by Raoult *et al.*, who analyzed clinical, laboratory and epidemiological features of 199 patients suffering from MSF. The authors reported severe form in 6% of patients and a mortality rate of 2.5%.[23] Therefore, even if organ involvement is a quite frequent condition (5-15% of cases), MODS/MOF should be considered an extremely rare event in *R. conorii* infection. The evidence of a proliferative thromboangiitis at level of arterioles and capillaries unleashed by *R. conorii* endotoxin could explain the organ involvement. Endothelial cell damage increases capillary permeability with edema and cells infiltrates, eventually leading to hypovolemia, ischemia, and bleeding. Involvement of different apparatuses seems to relate to tissue/organ previous injury and dysfunction (*e.g.*, ischemic heart disease, chronic obstructive pulmonary disease, *etc.*) or to a specific vascular tropism of endotoxins of different *R. conorii* strains.[22] In particular, abnormalities in the coagulation parameters are due to the direct action of *Rickettsia* or its toxin on both the vessels and megakaryocytes or platelets. The immune system response, with immune complexes formation and complement activation, triggers the intrinsic pathway coagulation.[24-26] Renal involvement is the most frequent organ abnormality, with pathological framework ranging from mild forms, with early albuminuria and hematuria, and modest increase in urea, to severe forms, with massive thromboangiitis requiring dialysis. Authors reported difference in kidney disease in *Rickettsia spp.* infection, ranging from 10 to 40% of the cases.[27,28] Quite frequently, physical examination proves a light hepatosplenomegaly, and laboratory examinations show a moderate increase in transaminases. However, acute hepatitis, sometimes with granulomatous appearance, always due to the endothelial cell damage, is considered a rare occurrence.[22,29,30] Other possible complications as encephalitis,[14,22,31-33] myocarditis[22,34,35] and pneumonia[22,36] are considered rare. In our case, the rapid onset of a MODS/MOF and the delayed appearance of cutaneous rash, together with the absence of the typical *tache noire*, certainly delayed the identification of the disease.

The second point that came to out attention in our case is the diagnostic and therapeutic delay due to the use of Weil-Felix agglutination test. In fact, the Weil-Felix agglutination test suffers poor sensitivity (ranging from 25% to 43%) and specificity (ranging from 37% to 62%),[37,38] and it has been replaced by ELISA and IFA, which proved a sensitivity of 80-90% and 93-98% respectively, and a specificity of about 80-85% for all of them.[4-8] The different techniques have been reviewed several times but IFA constantly results as the gold standard method.[4,6-8,39] It should be used to detect IgM and IgG separately; IgM titers >1/64 and IgG titers >1/128 are considered positive for *R. conorii* infection in suspected cases.[23,39] Both immunoglobulins' type usually became detectable 7-15

Table 3. Distribution of organ involvement in the epidemiological analysis by Bellissima *et al.* over 525 Mediterranean spotted fever patients.

Organ involvement	Number of patients (%)
Acute kidney failure	12 (2.2)
Acute hepatitis, without jaundice	6 (1.1)
Acute encephalitis	7 (1.2)
Myocarditis	5 (0.9)
Pneumonia	11 (2.1)
Massive pulmonary embolism	1 (0.2)
Gastrointestinal hemorrhage	2 (0.4)
Anemia	3 (0.6)
Impaired tolerance to carbohydrates	20 (3.8)

Modified from Bellissima et al., *2001.*[22]

days after symptoms' onset.[23-39] Other techniques, as isolation of bacteria and/or molecular polymerase chain reaction (PCR) to genome identification, which can be performed on blood, skin biopsies and ticks, are not routinely used because of their complexity and costs. Therefore, in clinical practice, they are reserved only in cases of extremely high clinical suspicion with all the other tests proving negative.[23,39-41] However, in the last decade, the increasing experience in molecular biology techniques has greatly extended the possibility of using real-time PCR to reduce diagnostic delays.[42] Angelakis *et al.* recently analyzed the sensibility and specificity of real-time PCR in detection of *Rickettsia* infection compared to isolation of *Rickettsia* spp. in skin biopsy. Skin biopsies and ticks from 145 patients with suspected rickettsiosis were screened using real-time PCR; positive samples were cultured in human embryonic lung fibroblasts using the centrifugation-shell vial technique. In addition, immunofluorescence was performed in 79 patients. Patients and ticks were classified as suffering from rickettsial disease where there was direct evidence of infection with a *Rickettsia* spp. using culture or molecular assays or, in patients, if serology was positive. Infection was diagnosed in 47 (32%) subjects, 41 by PCR and 12 by culture. Results analysis showed that 9 specimens proved positive both by real-time PCR and culture, whereas 32 culture negative specimens proved positive by real-time PCR analysis. The difference was statistically significant (P=0.0006), proving high sensibility and specificity in *Rickettsia* infection diagnosis by molecular biology technique. Only 3 patients proved negative both by PCR and by culture, being diagnosed basing only on immunofluorescence analysis. Comparison of culture and real-time PCR to serology was done for 26 patients; PCR sensitivity was 82% compared to serology whereas culture sensitivity was 29.4% compared to serology. Thus, according to these data, authors reported that even if culture remains critical for strain analysis it is less sensitive than serology and real-time PCR for the diagnosis of *Rickettsia* infections.[43] In 2012, Renvoisè *et al.* reported their 2-year-long experience in detection of *Rickettsia* by real-time PCR in France. Authors analyzed 643 clinical samples (corresponding to 465 different patients), detecting *Rickettsia* DNA in 45 of them. Authors proceeded by a two-step protocol: i) systematic primary screening for spotted fever group *Rickettsia* and targeted (on clinical and epidemiological features) typhus group *Rickettsia*; ii) second analysis was performed to identify *Rickettsia* species, whenever primary screening proved positive. Positive samples were detected mainly from cutaneous biopsies and swabs (31/45). The most frequently species identified were *Rickettsia africae*[15] and *R. conorii*.[9] Authors concluded that the widespread use of real-time PCR is inexpensive and reduces delay in the diagnosis of rickettsial infections.[42]

In our case, we delayed diagnosis due to the use of Weil-Felix agglutination test, which proved negative. Therefore, even if we suspected, in a first time, that the Weil-Felix reaction was negative because conducted too early, when antibody reaction could not be already detectable, the persistent negativity of the second Weil-Felix agglutination test showed us the diagnostic laboratory mistake. Unfortunately, history, simplicity and low cost make the agglutination reaction the most widely used diagnostic test for the detection of *R. conorii* infection. While this may be acceptable in the developing areas nations, in our opinion, it should be used no more in the most advanced countries.

Conclusions

We reported the case of a 59-year-old man affected by MSF, which rapidly evolved in a MODS/MOF. Organ involvement in *R. conorii* infection is not a rare condition, but evolution toward MODS/MOF, especially in a relatively young patient without severe comorbidity, is a rare event. Physicians should not delay diagnosis and treatment, which can easily control the infective status, allowing fast recovery of the patients, employing outdated, non-specific, non-sensible laboratory techniques, as the Weil-Felix agglutination test.

References

1. Colomba C, Saporito L, Siracusa L, et al. Mediterranean spotted fever in paediatric and adult patients: two clinical aspects of the same disease. Infez Med 2011;19:248-53.
2. Cascio A, Iaria C. Epidemiology and clinical features of Mediterranean spotted fever in Italy. Parassitologia 2006; 48:131-3.
3. Kularatne SA, Gawarammana IB. Validity of the Weil-Felix test in the diagnosis of acute rickettsial infections in Sri Lanka. Trans R Soc Trop Med Hyg 2009;103:423-4.
4. Prakash JA, Abraham OC, Mathai E. Evaluation of tests for serological diagnosis of scrub typhus. Trop Doct 2006;36:212-3.
5. De La Fuente L, Anda P, Rodriguez I, et al. Evaluation of a latex agglutination test for Rickettsia conorii antibodies in seropositive patients. J Med Microbiol 1989; 28:69-72.
6. Hazard GW, Ganz RN, Nevin RW, et al. Rocky mountain spotted fever in the eastern United States. N Engl J Med 1969;280:57-62.
7. Wächter M, Wölfel S, Pfeffer M, et al. Serological differentiation of antibodies against Rickettsia helvetica, R. raoultii, R. slovaca, R. monacensis and R. felis in dogs from Germany by a micro-immunofluorescent antibody test. Parasit Vectors 2015;8:745.
8. Sekhar WY, Devi S. The increasing prevalence of Endemic Typhus in Kuala Lumpur and an evaluation of a diagnostic ELISA dot test for the detection of antibodies to Rickettsia typhi. Singapore Med J 2000;41:226-31.

9. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine; 1992. Chest 2009;136:e28.
10. Montgomery AB, Stager MA, Carrico CJ, Hudson LD. Causes of mortality in patients with the adult respiratory distress syndrome. Am Rev Respir Dis 1985;132:485-9.
11. Sauaia A, Moore EE, Johnson JL, et al. Temporal trends of postinjury multiple-organ failure: still resource intensive, morbid, and lethal. J Trauma Acute Care Surg 2014;76:582-92.
12. Fröhlich M, Lefering R, Probst C, et al. Epidemiology and risk factors of multiple-organ failure after multiple trauma: an analysis of 31,154 patients from the TraumaRegister DGU. J Trauma Acute Care Surg 2014;76: 921-7.
13. Ferreira AM, Sakr Y. Organ dysfunction: general approach, epidemiology, and organ failure scores. Semin Respir Crit Care Med 2011;32:543-51.
14. Nakata R, Motomura M, Tokuda M, et al. A case of Japanese spotted fever complicated with central nervous system involvement and multiple organ failure. Intern Med 2012;51:783-6.
15. Wada K, Sakaeda H, Aono R, Chiya S. Fulminant Japanese spotted fever - the second fatal case in Japan. Kansenshogaku Zasshi 2008;82:77-81.
16. Kodama K, Senba T, Yamauchi H, et al. Japanese spotted fever associated with multiorgan failure. J Infect Chemother 2001;7:247-50.
17. Kuloglu F, Rolain JM, Aydoslu B, et al. Prospective evaluation of rickettsioses in the Trakya (European) region of Turkey and atypic presentations of Rickettsia conorii. Ann N Y Acad Sci 2006;1078:173-5.
18. Lee WS, Wang FD, Wang LS, et al. Scrub typhus complicating acute respiratory distress syndrome: a report of two cases. Zhonghua Yi Xue Za Zhi (Taipei) 1995;56:205-10.
19. Yamauchi T, Yamamoto S, Fukumoto M, et al. Early manifestation of septic shock and disseminated intravascular coagulation complicated by acute myocardial infarction in a patient suspected of having Legionnaires' disease. Kansenshogaku Zasshi 1998;72:286-92.
20. Devriendt J, Staroukine M, Amson R, et al. Malignant Mediterranean spotted fever. Report of a case with multiple organ failure, hypocalcemia, and euthyroid sick syndrome. Arch Intern Med 1985;145:1319-21.
21. Brouqui P, Parola P, Fournier PE, Raoult D. Spotted fever rickettsioses in southern and eastern Europe. FEMS Immunol Med Microbiol 2007;49:2-12.
22. Bellissima P, Bonfante S, La Spina G, et al. Complications of Mediterranean spotted fever. Infez Med 2001;9:158-62.
23. Raoult D, Weiller PJ, Chagnon A, et al. Mediterranean spotted fever: clinical, laboratory and epidemiological features of 199 cases. Am J Trop Med Hyg 1986;35:845-50.
24. Rao AK, Schapira M, Clements ML, et al. A prospective study of platelets and plasma proteolytic systems during the early stages of Rocky Mountain spotted fever. N Engl J Med 1988;318:1021-8.
25. Elghetany MT, Walker DH. Hemostatic changes in Rocky Mountain spotted fever and Mediterranean spotted fever. Am J Clin Pathol 1999;112:159-68.
26. Schmaier AH, Srikanth S, Elghetany MT, et al. Hemostatic/fibrinolytic protein changes in C3H/HeN mice infected with Rickettsia conorii - a model for Rocky Mountain spotted fever. Thromb Haemost 2001;86:871-9.
27. Shaked Y, Shpilberg O, Samra Y. Involvement of the kidneys in Mediterranean spotted fever and murine typhus. Q J Med 1994;87:103-7.
28. Sun IO, Kim MC, Park JW, et al. Clinical characteristics of acute kidney injury in patients with scrub typhus - RIFLE criteria validation. J Infect Chemother 2014;20:93-6.
29. Gupta R, Singh V. Indian tick typhus - an uncommon cause of hepatitis: a case report. J Clin Diagn Res 2014; 8:MD01-2.
30. Syhavong B, Rasachack B, Smythe L, et al. The infective causes of hepatitis and jaundice amongst hospitalised patients in Vientiane, Laos. Trans R Soc Trop Med Hyg 2010;104:475-83.
31. Colomba C, Imburgia C, Trizzino M, Titone L. First case of Mediterranean spotted fever-associated rhabdomyolysis leading to fatal acute renal failure and encephalitis. Int J Infect Dis 2014;26:12-3.
32. Aliaga L, Sánchez-Blázquez P, Rodríguez-Granger J, et al. Mediterranean spotted fever with encephalitis. J Med Microbiol 2009;58:521-5.
33. Duque V, Ventura C, Seixas D, et al. Mediterranean spotted fever and encephalitis: a case report and review of the literature. J Infect Chemother 2012;18:105-8.
34. Fukuta Y, Mahara F, Nakatsu T, et al. A case of Japanese spotted fever complicated with acute myocarditis. Jpn J Infect Dis 2007;60:59-61.
35. Shah SS, McGowan JP. Rickettsial, ehrlichial and Bartonella infections of the myocardium and pericardium. Front Biosci 2003;8:e197-201.
36. Schulze MH, Keller C, Müller A, et al. Rickettsia typhi infection with interstitial pneumonia in a traveler treated with moxifloxacin. J Clin Microbiol 2011;49:741-3.
37. Kularatne SA, Gawarammana IB. Validity of the Weil-Felix test in the diagnosis of acute rickettsial infections in Sri Lanka. Trans R Soc Trop Med Hyg 2009;103: 423-4.
38. Prakash JA, Abraham OC, Mathai E. Evaluation of tests for serological diagnosis of scrub typhus. Trop Doct 2006;36:212-3.
39. La Scola B, Raoult D. Diagnosis of Mediterranean spotted fever by cultivation of Rickettsia conorii from blood and skin samples using the centrifugation-shell vial technique and by detection of R. conorii in circulating endothelial cells: a 6-year follow-up. J Clin Microbiol 1996;34:2722-7.
40. Rovery C, Brouqui P, Raoult D. Questions on Mediterranean spotted fever a century after its discovery. Emerg Infect Dis 2008;14:1360-7.
41. Mert A, Ozaras R, Tabak F, et al. Mediterranean spotted fever: a review of fifteen cases. J Dermatol 2006;33: 103-7.
42. Renvoisé A, Rolain JM, Socolovschi C, et al. Widespread use of real-time PCR for rickettsial diagnosis. FEMS Immunol Med Microbiol 2012;64:126-9.
43. Angelakis E, Richet H, Rolain JM, et al. Comparison of real-time quantitative PCR and culture for the diagnosis of emerging Rickettsioses. PLoS Negl Trop Dis 2012;6: e1540.