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Diversity of Life-Threatening Complications due to Mediterranean Spotted Fever in Returning Travelers

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Background. Mediterranean spotted fever (MSF) is a tick-borne infection caused by *Rickettsia conorii conorii* mainly endemic in the Mediterranean Basin. Although usually considered as a benign disease, severe forms of MSF have been sporadically reported.
Methods. We report on three patients who developed severe MSF complications after a stay in Morocco. Literature was reviewed to assess the frequency and pattern of MSF complications in the largest reported case series in endemic countries.
Results. Each of our three patients diagnosed with MSF presented with a different complicated course: one with meningoencephalitis, one with lung embolism and one with septic shock and multi organ failure. In published series, rate of complications (defined as severe organ involvement) ranged from 1% to 20%. However, study designs and settings were highly variable and did not allow for relevant comparisons. Meningoencephalitis and shock with multi organ failure were the most frequently observed complications. Mortality of severe course was up to 20% in some series.
Conclusion. Severe organ involvement is not infrequent in patients with Mediterranean spotted fever and fatal outcome is regularly reported. Because presentations of complicated course may be extremely diverse, a high index of suspicion is required in febrile patients with potential exposure, in particular if skin rash and/or eschar are found. Early appropriate antibiotherapy is crucial to improve outcome.

Advanced molecular tools have brought new insights on the complex worldwide epidemiology of rickettsial infections. New rickettsial pathogens are increasingly recognized while knowledge about long-known rickettsioses evolves continuously.[1] Mediterranean spotted fever (MSF), first described in 1910, is a disease caused by *Rickettsia conorii* and transmitted by the brown dog tick (*Rhipicephalus sanguineus*). This infection is mainly endemic in the Mediterranean area but has been also sporadically reported in sub-Saharan Africa and Southern Asia.[2] On the basis of genome sequencing, it has been proposed in 2005 to divide the *R conorii* species in the following subspecies: *R conorii conorii*, *R conorii israelensis*, *R conorii caspia*, and *R conorii indica*.[3] *Rickettsia conorii conorii* (strain Malish) is now considered the etiologic agent of MSF, whereas the other subspecies cause diseases with distinct epidemiological and clinical features (respectively Israeli spotted fever, Astrakhan spotted fever and Indian tick typhus).

MSF has long been considered as a benign disease, but since the early 80 s severe forms and fatalities have been regularly described.[4]

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Methods

We report on three cases of MSF with very diverse severe presentations observed in Moroccan patients returning to Belgium after a visit to friends and relatives in their country of origin. We completed our findings by a literature review in Medline and Pubmed between 1980 and 2009. We identified the largest studies (more than 50 cases) on MSF conducted in endemic regions and published in the English, French, and Spanish literature. We then extracted the rates of complication (defined as any end organ failure) and fatality as well

as the patterns of severe course reported in those case series.

Results

Case Reports

Case 1

A 49-year-old Moroccan patient living in Belgium developed in July 2004 fever and headache while visiting his family on the Mediterranean coast of Morocco (near Tangier). Despite a treatment with ampicillin prescribed by a local physician, he had to be admitted 6 days later in Tangier because of high fever, skin rash, and altered consciousness. Laboratory testing showed a normal leukocyte count (8,700/μL), a severe thrombocytopenia (34,000/μL), an acute kidney failure (creatinine 4.3 mg/dL; blood ureum nitrogen 169 mg/dL), and abnormal liver tests (total bilirubin of 2.9 mg/dL; alanine transaminase [ALT]: 157 IU/L; aspartate transaminase (AST): 214 IU/L). A computed tomography (CT) scan of the brain was normal. A chest X-rays revealed an infiltrate at the right upper lobe. The clinical condition worsened during the next few days with a coma 7/15 on the Glasgow scale, disseminated petechial lesions, hypotension, and hypoxemia. Examination of the cerebrospinal fluid (CSF) was unremarkable. Patient was stabilized by mechanical ventilation, repeated hemodialyses, and intravenous ceftriaxone, amoxicillin–clavulanate and ciprofloxacin. Four days after admission, he was transferred to the Saint-Pierre University Hospital, Brussels, Belgium. He was still febrile (38.5°C) and slightly confused with neck stiffness, a purpuric rash predominating on his thorax and upper limbs and a flaccid quadriplegia. A magnetic resonance imaging of the brain showed a meningeal contrast enhancement and a signal hyperintensity in the right frontal lobe. A new CSF examination revealed 95 nuclear elements (70% of lymphocytes) and a protein level of 106 mg/dL. Direct examination, cultures and molecular investigations on CSF were all negative. Ceftriaxone, ampicillin, and doxycycline were given. Clinical condition improved slowly with recovery of a normal consciousness. Paraparesia and sphincter impairment persisted at discharge but finally recovered over a few weeks time. At admission in Brussels, immunoglobulin (Ig)G titer against *R conorii* was undetectable (<1/40) by immunofluorescence (IF) but reached 1/640 10 days later. No seroconversion against other relevant pathogens was observed.

Case 2

A 62-year-old Moroccan patient, resident in Belgium, was admitted in September 2007 at the University Hospital of Antwerp, Belgium because of high fever, cough, thoracic pain, dyspnea, and skin rash. Symptoms developed 3 days after he came back from a 1-month trip to the Mediterranean coast of Morocco in Nador, where he visited friends and relatives. Before admission, he had been given successively cefuroxime axetil and amoxicillin–clavulanate by his family doctor, without improvement. At admission, patient had fever (38.8°C) and a generalized purpuric rash. Pulmonary auscultation revealed wheezes and crackles at the right base. Blood test showed a normal leukocyte count (5,600/μL), a lowered platelet count (144,000/μL), an elevated level of C-reactive protein (CRP: 22 mg/dL), slight elevation of ALT and AST and an elevated level of lactate dehydrogenase (LDH: 1,645 IU/L). Arterial blood oxygen was decreased to 66 mmHg, and associated with hypocapnia and respiratory alkalosis. An electrocardiogram was normal. Echocardiography revealed a slightly elevated pressure of the pulmonary arteries (27 mmHg). A CT angiographic scan of the thorax demonstrated a thrombosis in the secondary tree of the lower right lobe and peripheral lung thromboses. A duplex of the lower limbs did not show any deep venous thrombosis. Treatment with low-weight heparin and doxycycline was initiated. Skin biopsy showed a neutrophilic infiltration around and in the blood vessels suggestive of leukocytoclastic vasculitis. Recovery was fast and uneventful and patient was discharged after 9 days. At admission, all relevant serological tests were negative. Two weeks later, IF serology demonstrated an IgG titer of 1/1,280 against *R conorii*. A protein C deficiency was also diagnosed.

Case 3

A 61-year-old Moroccan living in Belgium was repatriated from Morocco in September 2007 and admitted in the University Hospital of Antwerp, Belgium because of multi organ failure. He was visiting his family in Tetouan and in Nador (Mediterranean coast of Morocco) when he became abruptly ill. He was hospitalized in an intensive care unit in Morocco with high fever, jaundice, severe upper intestinal bleeding, and septic shock. Blood results showed at that time elevated white blood cells count (17,600/μL, comprising 95% of neutrophils), a low platelet count (48,000/μL), an elevated CRP level (20 mg/dL), a kidney failure (level of creatinine: 2.5 mg/dL), and liver test disturbances (ALT: 102 IU/L, total bilirubin 6.3 mg/dL, conjugated bilirubin 4.4 mg/dL). Fluid resuscitation, inotropic agents, hemodialysis, proton-pump inhibitors, and amoxicillin–clavulanate were administered and the patient was transferred to our institution 10 days later. At admission he had no more fever (37.2°C), was hemodynamically stable and cognitively fine. Patient was too weak to stand alone, but no focal neurological defect was found. Jaundice and a slight purpuric rash were noticed. Doxycycline was added to the ongoing treatment. A gastroscopy revealed a large gastric ulceration with stigma of recent bleeding. Clinical and laboratory evolution was quickly favorable thereafter.

On admission in our institution IF assay was positive for *R conorii* (IgG titer: 1/640) and *R typhi* (1/320). Paired

Table 1 Rates of complication and fatality in patients diagnosed with Mediterranean spotted fever in the largest reported series (>50 cases)

Study location (reference)	Study period	Setting and type of patients	Number of patients	Method of diagnosis	Severe course, *n* (%) (study definition); main complications*	Fatality rate, *n* (%)
South of France[15]	1983–1984	Hospital	142	Serology	7 (5) (stay in intensive care); meningoencephalitis, $n = 6$; respiratory failure, $n = 1$	2 (1.5)
South of France[10]	1981–1988	Hospital	412	Serology	25 (6) ("malignant form"); no clinical detail	Not reported
Spain[5]	1983	Hospital	71	Serology	6 (8) (shock)	4 (6)
Spain[11]	1981–1988	Hospital	246	Serology	18 (7) (one organ failure or local criteria of severity);altered cousciousness, $n = 11$ respiratory failure, $n = 1$ shock, $n = 1$	0
Sicily[7]	1984–1996	OPD/only children	645	Serology	Not reported	0
Spain[12]	1986–1994	Hospital	86	Clinical diagnosis ± serology	19 (22) ("severe complications")renal failure, $n = 12$ uppergastrointestinal bleeding, $n = 5$ respiratory failure, $n = 4$ stroke, $n = 3$	0
Croatia[14]	1982–1999	Hospital	63	Serology	Not reported	0
Spain[6]	1989–1999	Hospital	144	Serology	0 (no definition)	0
Portugal[9]	1994–1998	Hospital	105	Clinical diagnosis	Not reported	19 (18)
Sicily[8]	1997–2004	OPD/only children	415	Clinical diagnosis ± serology	1 (0.2) (meningoencephalitis)	0
Algeria (Oran)[13]	2004–2005	OPD/Hospital	167	Serology, PCR of eschar	22 (13) ("much altered state of health") meningoencephalitis, $n = 18$ respiratory failure, $n = 5$ shock, $n = 12$ renal failure, $n = 7$	6 (3.5)

OPD = outpatient department; PCR = polymerase chain reaction.
*More than one complication possible per patient.

serology 2 weeks later confirmed a more than fourfold increase of the titer against *R conorii* (>1/2,560), but not against *R typhi* (1/640).

Discussion

The three reported cases of MSF acquired in Morocco presented with very different malignant courses: the first one with meningoencephalitis, the second one with lung embolism, and the third one with septic shock and multi-organ failure. No fatality occurred but the first patient experienced prolonged and serious neurological impairment.

In historical series before antibiotic use, mortality rate of MSF was below 1% and severe forms were described very sporadically.[2] Since the eighties however, complicated cases have been increasingly reported. Table 1 summarizes the main findings of the largest published series.[5–15] This overview has however several limitations. First, comparisons between studies are impossible because they differ widely in terms of location, setting (mostly hospital-based), design (mostly retrospective), study participants (adults and/or children), recruitment bias, diagnostic criteria for MSF (clinical—classic immunofluorescence serology—newer reference methods), and case definitions of severe course. This last definition is particularly variable between series, ranging from "hospital admission"[13] to "severe organ involvement"[8,12] or "admission in intensive care."[15] We have tried therefore to extract from each publication the major complications, but clinical details were not always available and several syndromes were maybe present in combination. Also, since diagnosis relied in almost all series on serological testing (paired serology or single serology with suggestive MSF features), species other than *R conorii* may have been included due to cross reaction, like for example *R aeschlimannii* in Spanish series[16] or *R slovaca* in Sicilian studies.[8] This could even explain that subsets of patients were observed with atypical MSF features like multiple eschars or eschars on children scalps.

Beyond the uncertainties due to different study definitions, reported rates of severe organ involvement varied extremely, from less than 1% in pediatric series to 5% in large French studies, and up to 15% to 20% in some reports from the Iberian Peninsula and from Algeria. Mortality rates ranged from 0% to 3% in all published series, except in one retrospective hospital-based study from Portugal (with clinical diagnosis) where 20% of fatalities were reported (with a peak of 33% of admitted patients in 1997).[9] Complications and death have been associated with advanced age, debilitating underlying conditions and delay in appropriate treatment.[17] It is however established that disease severity varies according to time and geographic location.[4] Reasons are unclear

but differences may be due to variability in defining a complicated course, recruitment bias, changes in *R conorii conorii* virulence,[4] or local contribution of *R conorii* subspecies possibly more pathogenic.[18–22]

Meningitis and encephalitis have been classically reported as possible complications of MSF. However, a recent literature review has identified only seven cases properly documented.[23] Similarly to our first case, all patients presented with complications like kidney failure, respiratory distress or hypotension besides the neurological manifestations. Dysfunction of the central nervous system included signs as diverse as stupor ($n = 5$), seizure ($n = 3$), incontinence ($n = 2$), ataxia, aphasia, flaccid quadriplegia or paraplegia ($n = 1$ for each sign). Three patients died and three of those four who survived developed severe sequels. In a recent study, 7% of Algerian patients diagnosed with MSF presented with "major neurological manifestations", and the fatality rate exceeded 50% in this subgroup.[13]

Lung embolism has been exceptionally described in MSF,[2] although pulmonary involvement seems rather frequent (infiltrates and pleural effusion in up to 25% of the Algerian cases).[13] In our second case, the lung thromboses might have been due to the rickettsia-induced vasculitis (evidenced also in the skin biopsy) or to some thrombophilic phenomenon precipitated by the systemic inflammation and the protein C deficiency. No deep venous thrombosis could be found and the angiographic findings did not allow a clear-cut conclusion. Clinical recovery seemed however to have been fastened by the addition of doxycycline to the anticoagulation treatment.

Septic shock and multi organ failure were observed in our third case. This patient had no sign of encephalitis but presented also with a life-threatening gastric bleeding. Shock and multi organ failure were reported in 7% of the MSF cases from Algeria and were most often associated with severe neurological manifestations and high fatality rate.[13] Other fatalities reported in the literature presented also with severe intestinal hemorrhage.[2]

Infections by rickettsial pathogens are characterized by the invasion and multiplication in vascular endothelial cells, resulting in a widespread infectious vasculitis. This has been confirmed by autopsy studies demonstrating disseminated perivascular lymphohistiocytic infiltrates in all organs associated with micro-hemorrhages and micro-thrombi. This ubiquitous process explains the protean clinical manifestations and the wide spectrum of complications according to the predominantly injured organs. Besides the major complications observed here, others have also been reported like myocarditis, pericarditis, uveitis, retinitis, myelitis and Guillain-Barré syndrome.[24–27] Of note none of our patients had any host risk factor for complicated course.

The major limitation of our observations is the use of standard serological tests for diagnosis. Cross-reactions with other or emerging rickettsiae of the spotted fever group are possible, although the clinical features and the serological results convincingly support the diagnosis of MSF in each case. However, the assays we used did not allow differentiation between subspecies of *R conorii*. Molecular techniques might have identified another subspecies like *R conorii israelensis*, which has been found in some fatal cases of MSF in Portugal and Italy and is suspected to be more pathogenic, although this is debated.[28] However, this subspecies has never been reported to date in Morocco to our knowledge.[29]

Finally, the most striking observation is that the diagnosis of MSF had been missed in all three patients when they initially sought medical attention in the endemic country. Similarly, the diagnosis was not considered in the non-endemic emergency wards after repatriation. For each case, the skin rash and recent exposure did lead the infectious disease specialists to initiate a presumptive therapy with doxycycline, which resulted in turn in a prompt clinical improvement. Of note, no inoculation eschar was noted in any case by the experienced clinicians and despite active search. A maculo-papular or purpuric rash is observed in almost 100% of the MSF cases, but the presence of an eschar is reported in 20% to 90% of the cases according to the series.[4] In addition, all three patients presented very late in Belgium, at a moment the inoculation eschar may have disappeared.

Conclusion

MSF presents sometimes with a malignant, life-threatening, course. Since complications may be extremely diverse, clinical awareness is crucial when facing a traveler returning from Southern Europe or Africa and presenting with fever and skin rash or with fever and eschar(s). Early administration of antibiotics with intracellular activity gives a much higher chance to get prompt recovery. Molecular techniques should become more widely available in reference travel clinics, to help refining the complex and evolving rickettsial epidemiology in mobile populations. For the patient management, these diagnostic tools are presently not sensitive enough for blood samples but may be helpful when performed on a skin biopsy of the edge of the eschar or of a spot of the rash.

Declaration of Interests

The authors state they have no conflicts of interest to declare.

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