ASSESSMENT OF THE ORGAN SYSTEM INVOLVEMENT IN THE MALIGNANT FORMS OF SPOTTED FEVER RICKETTSIOSIS

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ABSTRACT

PURPOSE: Mediterranean spotted fever (MSF), a spotted fever rickettsiosis caused by *Rickettsia conorii* has become a significant health risk for suffering people and international travelers. The purpose of the study was to outline the prognostic factors of the fatal outcome in the diseased patients. **MATERIALS AND METHODS:** In this report, we present the organ system involvement in 55 patients (19 fatalities and 36 survivors) with malignant forms of the disease. **RESULTS:** Based on our data, the most frequently involved organ systems of malignant cases were: central nervous system 100%, liver 92.72%, kidneys 60%, lungs 58.18%, myocardium 30.9%, and gastrointestinal tract 23.63%. The conducted histopathological investigations revealed lethal complications: encephalitis, brain edema, acute respiratory distress syndrome, non-cardiogenic lung swelling, acute myocarditis, gastrointestinal bleeding, hemorrhagic-necrotizing pancreatitis and acute renal failure. **CONCLUSION:** The main prediction factors for mortality in malignant MSF patients were the vital organ system complications. In the past, overlooked as a serious disease, at present it is known that MSF was wrongly considered a benign condition.

Key words: Spotted fever rickettsiosis, *Rickettsia conorii*, fatal forms, organ system complications

INTRODUCTION

Mediterranean spotted fever (MSF), known as Marseilles fever or Boutonneuse fever is a rickettsial disease endemic for the countries along the Mediterranean coast (South Europe and North Africa). However, a growing number of cases are reported from Central and Eastern Europe (1, 2). As a result of globalization and growing tourism, imported cases of MSF are reported in many non-endemic countries and regions. Molecular instruments as PCR and sequencing have identified the responsible for the disease rickettsial agent *Rickettsia conorii subsp. conorii*, strain Malish Seven (1). The main

epidemiological feature of MSF is the transmission of rickettsiae to humans in the endemic regions by the bite of the brown dog tick *Rhipicephalus sanguineus* during the favorable for tick's biology spring-summer season. Another important epidemiological determinant is the human contact with tick's intermediate hosts - domestic and stray dogs (3, 4). The main clinical signs and symptoms of MSF are: skin eschar (black spot or tache noire) at the site of the tick bite, fever and flu-like manifestations as headache, adynamia, anorexia, myalgia, etc., emerging 3-5 days before the onset of papular or maculopapular rash over the trunk and extremities, involving the hands and feet.

Known in Europe since the beginning of the twentieth century, MSF has long been considered a benign disease. In the early 1980s, D. Raoult et al. reported a patient with a fatal outcome due to MSF and used the term «malignant» for the most severe forms

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of the disease (5). In 1980s and 1990s, the disease was particularly common in many European countries, and severe - "malignant" forms, including lethal cases have been observed. The mortality rate reached 54.5% in hospitalized patients with neurological manifestations and multiorgan involvement (6). Currently it is known that MSF is, at least as severe as Rocky Mountain spotted fever (RMSF).

In Bulgaria MSF was described in 1948 and for over two decades (1948-1972) had presented as a mild to moderate disease without registered mortality (7). Following a 20 year pause, during which the disease was considered eliminated, it reemerged in the early 1990s and rapidly affected thousands of people in the endemic regions. During this second wave various forms of the disease were observed, and very severe, actually "malignant" forms were reported, some of them even fatal. In one of our investigations (which included 549 patients in the largest endemic region of Bulgaria – the city of Plovdiv and suburbs lethality rate in all treated patients was 3.46%, and mortality in malignant forms reached 34.54% (8).

MATERIAL AND METHODS

Fifty five patients (30 men and 25 women) with malignant forms of MSF were involved in the study. They were divided into two groups: Group I comprised 19 fatalities with mean age 59.55 ± 4.09 years; Group II comprised 36 survivors with mean age 47.22 ± 5.81 years (Mean $\pm$ SEM), $p > 0.05$). MSF was proven by the indirect immunofluorescent assay (IFA), with at least a fourfold increase in the antibody titer to a specific *R. conorii* antigen (IFA test *Rickettsia conorii*—Spot IF, BioMerieux, Marcy L'Etoile, France). IgG titres of ≥ 128 and /or IgM titres of ≥ 64 were considered indicative of acute infection [9]. Diagnostic confirmation by IFA was performed at the Reference Laboratory of Rickettsiae in Sofia.

Histomorphology: Complete post-mortem examinations were performed in all patients with lethal outcome of the disease. The specimens of liver, lung, kidneys, stomach, pancreas and brain were fixed in a 4% neutral buffered solution of formaldehyde, embedded in paraffin, sectioned at 5 micrometers thickness, and processed by staining with hematoxylin/eosin for evaluation of histopathology.

RESULTS AND DISCUSSION

A number of studies have reported severe/malignant MSF and complications (5, 6, 10-13, 15, 16). In order to standardize a definition of the disease forms in severity, we developed a classification of MSF clinical forms and proposed a scheme based on a set of criteria, defining severity (8). In our research, malignant forms of MSF were defined as "Forms with multi-organ involvement (malignant)". All studied 55 patients had a sudden onset with fever, chills, myalgia, headache, and other flu-like symptoms. In all patients, three to four days after the onset of symptoms, a specific maculopapular rash developed, typically starting on the trunk and spreading out to the extremities. It involved the hands and feet in 49 patients (89.09%). Forty one (74.5%) patients presented with tache noire, and conjunctiva was the likely port of entry in 4 cases. Cracks on fingers, incurred in the process of tick removal from pet dogs were the site of penetration in 10 cases. Involved organ systems, comparatively between the two groups are shown in **Table 1**.

CNS involvement is the acknowledged hallmark of malignant forms of MSF (10-13). Altered mental status of variable degree was present in all of our patients, ranging from cognitive slowing and somnolence to apathy or confusion termed by classical authors as typhus state or «Status typhosus ». The latter was equally present in the fatality group similarly to MSF survivor group. Typhoid mental condition is likely to progress to more severe CNS deterioration as delirium, stupor and coma, indicative of meningoencephalitis and/or brain edema. These symptoms were significantly more frequent in the deceased patients, compared to survivors and consequently appeared as risk factors for patients with malignant MSF.

Pulmonary involvement, presenting as interstitial pneumonia, was often seen in MSF patients (14). It was present in 29(52.72%) of our malignant forms of MSF, without statistical difference between the two studied groups. Acute respiratory distress syndrome (ARDS) however was present only in the group of lethality and appeared as one of the most important risk factors for death (15, 16).

Table 1. Comparative assessment of organ system involvement in fatalities (group I) and survivors (group II) in malignant Mediterranean spotted fever forms.

	MSF total cases n=55		MSF lethal cases n=19 Group I		MSF survivors n=36 Group II		Fisher's exact test		
	n	%	n	%	n	%	p	OR	95% CI
CNS involvement:	55	100.00							
<i>Mental confusion - typhus state</i>	49	89.09	19	100.00	30	83.33	= 0.08	8.311	0.44 – 156.09
<i>delirium/seizures, stupor/coma</i>	24	43.63	12	63.15	12	33.33	= 0.04	3.429	1.07 – 10.95
Pulmonary involvement:	32	58.18							
<i>interstitial pneumonia</i>	29	52.72	13	68.42	16	44.44	= 0.15	2.708	0.84 – 8.72
<i>ARDS*</i>	3	5.45	3	15.78	0	0.00	= 0.03	15.485	0.75 – 317.44
<i>acid-base balance hard violation</i>	17	30.90	13	68.42	4	11.11	<0.0001	17.333	4.19 – 71.73
Myocardial involvement:	17	30.90							
<i>ECG abnormalities</i>	16	29.09	8	42.10	8	22.22	= 0.21	2.545	0.76 – 8.48
<i>myocarditis**</i>	17	30.90	13	68.42	4	11.11	<0.0001	17.333	4.19 – 71.72
Hepatic involvement:	51	92.72							
<i>ALT/AST increased</i>	51	92.72	16	84.21	35	97.22	= 0.11	0.152	0.014 – 1.58
<i>jaundice</i>	35	63.63	11	57.89	24	66.66	= 0.58	0.687	0.220 – 2.16
Digestive tract involvement:	13	23.63							
<i>gastrointestinal bleeding</i>	8	14.54	6	31.57	2	5.55	= 0.01	7.845	1.40 – 43.97
pancreatic involvement	5	9.09	4	21.05	1	2.77	= 0.04	9.333	0.96 – 90.68
Renal involvement:	33	60.00							
<i>very high urea and creatinine levels</i>	33	60.00	17	89.47	16	44.44	=0.001	10.025	2.13 – 52.95
<i>acute renal failure</i>	30	54.54	16	84.21	14	38.88	=0.001	8.381	2.05 – 34.11

Legend: CI - Confidence interval; OR – Odds Ratio; ARDS - acute respiratory distress syndrome;

MSF – Mediterranean spotted fever

Myocarditis is an uncommon, however severe occurrence in MSF, and only few cases have been reported in the literature (17, 18). Myocardial involvement was found in about one third of the patients with malignant form of MSF. Myocarditis, diagnosed clinically and instrumentally, as well as based on histology proved to be a risk factor for mortality as it appeared several times more frequently in deceased than in survivors from malignant MSF.

Several studies have stated a high frequency of liver functional impairment in the course of MSF (19). Based on increased ALT and AST activity, complicity of the liver occurred in almost all patients, and jaundice - in more than half of them. However, both findings showed no prevalence in deceased patients compared to survivors from malignant MSF. Hemorrhages in the gastrointestinal tract are serious, although considered uncommon complication of vasculitic changes in

malignant forms of MSF (20-22). Gastrointestinal bleeding was a real risk factor for fatal outcome in our patients. Severe pancreatic damage (histological data in 4 deceased patients) and clinically suspected in only one of the survivors, was also a serious risk factor for death in malignant MSF forms.

Involvement of the kidneys was found in approximately 60% of the patients with malignant MSF. It presented with a significant increase in the serum urea and creatinine levels. Acute renal failure (ARF) was demonstrated at approximately the same rate. Both conditions were nearly twice as common in deceased compared to surviving patients and presented real risk factors for the lethal outcome in the most severe forms of MSF, the so-called malignant forms (23, 24).

CONCLUSION

Long time overlooked as a serious disease, at present, it is known that MSF had a false benign reputation. In this report we managed to identify the prognostic factors for mortality or survival in malignant forms of MSF. This approach is justified as the diagnosis in such cases is frequently a problem, resulting in delayed treatment. Early diagnosis and appropriate antibiotic treatment may reduce the risk of complications.

Conflict of Interests: There is no conflict of interests regarding the publication of this paper

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