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(CASE REPORT)

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Marseilles fever: Common knowledge and clinical case presentation

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Abstract

Mediterranean spotted fever (MSF), also known as Marseilles fever (MF) is a tick-borne infectious disease caused by Rickettsia conorii subspecies conorii (R conorii), Gram-negative, intracellular bacterium. It is transmitted by the brown dog tick Rhipicephalus sanguineus that is vector and reservoir of R. conorii. MSF is characterized by diverse clinical manifestations, presenting with both typical and atypical features, making the early diagnosis of the disease challenging. Mild clinical forms are usually observed in children, while complications of MSF are more common in patients with underlying disease or in elderly persons. In Bulgaria, Mediterranean spotted fever is subject to mandatory registration, according to the current Regulation 21 of 2005 on the procedure for registration, notification and reporting of infectious diseases.

Keywords: Mediterranean spotted fever; *Rickettsia conorii*; Rhipicephalus sanguineus; Clinical manifestations; Diagnosis

1. Introduction

Historically, Mediterranean spotted fever (MSF) was firstly reported in North Africa (Tunis) in 1910 as a clinical syndrome named „fièvre boutonneuse" or macular fever, due to the accompanying rash. The typical inoculation eschar, ("tache noire" or black spot), was described in 1925 in Marseille by Boinet and Pieri [1]. In 1930, Durand and Conseil showed the role of the dog tick R. sanguineus in disease transmission. In 1932, Brumpt discovered the causal agent, a rickettsia that he named in honor of Connor: R. conorii [2]. Experimental work by Durand and Conseil and Blanc and Caminopetros demonstrated that the Rhipicephalus sanguineus serves both as the vector of the disease and reservoir of the agent. The etiological agent of MSF was named Rickettsia conorii in 1932.

MSF is an endemic disease. It is most commonly found in the Mediterranean region of Europe, select regions surrounding the Black Sea, sub-Saharan Africa and India. Among the European countries with relatively high R. conorii infection rates are Portugal, Spain, France and Italy [3]. In temperate regions like Bulgaria, MSF is found during summer. In tropical and subtropical areas is found throughout the year. Epidemiological data reveal that the incidence of MSF to follow a seasonal endemicity, as most reported cases in endemic areas to emerge in the summer. High temperatures affect the incidence of the disease by modulating tick biological activity. The number of human cases is typically highest between June and October, coinciding with the peak tick season [4]. Seroepidemiological studies in Europe and Mediterranean countries have shown that R. conorii prevalence in people living in rural regions (10%-60%) is higher than in towns (2–30%) [5]. Frequency of MSF cases varied, presenting with peaks and valleys during the past few decades.

In Bulgaria, the infection was identified for the first time in 1948 by Vapzarov in Plovdiv region [6]. MSF occurred in two epidemic waves, the first being between 1948 and 1970. MSF cases started to sharply decrease at the beginning of the 1960s and completely disappeared in the 1970s. The second epidemic wave began in the early 90's of the last

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century the disease spreading over the endemic regions of the Maritza river and the Black Sea coast. In 1995, a peak of disease with 236 cases was noticed in the country and reached 716 cases in 1997 [7]. MSF is considered to be a wide-spread rickettsiosis in Bulgaria and occurs along both the coastal and inland districts, with the highest incidence reported from south-eastern and southern areas of the country including the Burgas, Varna, Sliven, Stara Zagora, Haskovo, Jambol, Plovdiv and Pazardjik regions. In Bulgaria annually cases of Mediterranean spotted fever are reported. During the period from 2000 till 2003 a total of 336 patients with Mediterranean spotted fever were hospitalized in the First Clinic of Infectious Diseases at St. Marina University Hospital of Varna, of them 26.78% older 60 years [8].

Following skin inoculation, Rickettsia spread via lymphatics into the circulation. The pathophysiologic hallmark of R conorii infection is the invasion of endothelial cells of small and medium blood vessels, causing endothelial injury and tissue necrosis, which is illustrated by the „tache noire'' or eschar at the tick bite site. The development of a systemic vasculitis is the main pathogenetic factor in the origin of systemic complications.

MSF typically has an incubation period of 5 to 7 days following the tick exposure. The tick bite is usually painless and may not be noticed if it occurs in an inconspicuous location. There are 3 periods of disease: initial period (from the first days of fever to rash appearance, it last 2-4 days); height of disease (from rash appearance to normalization of body temperature, it last 3-10 days); recovery period (after normalization of body temperature). MSF is typically characterized by the classical triad of symptoms: fever, diffuse maculopapular skin rash and a „tache noire'' (black spot), at the site of the tick bite. The fever and rash being the most common symptoms reported. This rash is classically spread to the palms and soles and spares the face, and is most commonly maculopapular. The characteristic eschar has a variable frequency. In most cases it is one of the main clinical manifestations of MSF, presenting in ≥60% of cases [9]. The black spot is painless, sometimes necrotic. Headache is one of the typical symptoms of the disease in adults [*10*]. Its lower frequency in children contributes to the milder clinical presentation in this age group. Atypical clinical features may also be present. Furthermore, leukopenia, thrombocytopenia, increased transaminases, and decreased serum ion (Na+, K+, and Ca2+) levels are common nonspecific laboratory findings in MSF [11].

The evolution of the disease is favorable in most cases, and mortality is low. Traditionally, MSF was characterized as a benign rickettsiosis, but severe and "malignant" forms and fatalities have been described [*12*]. Severe complications can occur in about 6–10% of cases, often resulting from delayed diagnosis [13]. The mortality rate is usually estimated at around 2.5% [14]. The disease affects all age groups, and usually has mild to moderate course. Children seem to be less susceptible to severe complications of MSF than adults. Children accounted approximately for 70% of the disease mild forms [15]. Identified risk factor s for severe forms include older age, underlying disease, immunosuppression, chronic alcoholism, and glucose-6-phosphatase dehydrogenase (G6PD) deficiency, delay in treatment and inadequate antimicrobial therapy. Death from malignant MSF has been associated with delays in diagnosis (>5 days) and treatment (>10 days). Promptly administered antibiotic treatment shortens the symptomatic period of MSF and prevents the appearance of severe complications.

Several methods exist for the diagnosis of MSF. Serological tests are widely used and molecular techniques have become increasingly available. There is no reliable test to diagnose the infection in its early stages. The most specific method for the diagnosis of R. conorii infection is the identification of the agent, either by immune staining in tissue specimens or by polymerase chain reaction (PCR) [16]. Serologic testing is the mainstay of laboratory diagnosis. There are several tests available, including Immunofluorescent assay (IFA), Enzyme-linked immunosorbent assay (ELISA) and Chemiluminescent immunoassay (CLIA).

The detection of antibody to R. conorii by serological test is the most available laboratory method to diagnose Mediterranean spotted fever in acute and convalescent sera. Both IgM and IgG can be detected 7–15 days after the onset of the disease [17,18]. In a study in Turkey, 77% of patients had a 4-fold increase in R. conorii antibodies in two sera collected within a 2-week interval using the IFA test. They also showed that 73% of skin biopsy samples tested positive for ompA and gltA gene PCR [19]

Doxycycline is considered first-line antibiotic of choice for MSF. Macrolides such as azithromycin and clarithromycin are efficacious in children and pregnant women for whom doxycycline is contraindicated [20]. Patients with a more benign progression are treated with antibiotics for 7 days. Those with more progressive symptoms are usually treated for 14 days.

Prophylaxis in endemic areas includes obligatory registration of the dogs, the processing of the dogs and the places of the ticks. Preventative measures focus on minimizing contact with ticks, such as wearing protective clothing and using insect repellent.

2. Case report

On July 2019, a 48-year-old woman, previously healthy woman presented to the infectious clinic with fever (40°C), which lasted a few days and was associated with myalgias, general weakness and malaise.

Since the patient reported the appearance of pale stools (hypocholia) and dark urine, she was admitted with suspicion of unspecified viral hepatitis. The examination of hepatitis markers for HAV, HBV, HCV and HEV rejected the initial (admission) diagnosis. On the second day of hospitalization, a maculopapular rash appeared on the body, which raised suspicion of Marseille fever, despite the absence of an epidemiological history and characteristic eschar.

The physical examination in the emergency room revealed a fever of 40 °C, hyperemic throat, hypotension (90/60 mmHg) and hepatomegaly. Laboratory tests upon admission revealed an elevated C-reactive protein (209.8 mg/L; normal value 0-5), lymphopenia, thrombocytopenia (108 10^9/l; normal value 140 - 440), anemia, and abnormal liver function tests (alanine aminotransferase 78 IU/L, aspartate aminotransferase 62 IU/L; normal value 5-35), elevated Creatine phosphokinase (CPK) - serum (236 U/l; normal value 15 - 180).

Rickettsia conori serology by indirect chemiluminescent immunoassay (Rickettsia conori VirClia® IgG /IgM Monotest, Vircell, Spain) retrospectively confirmed the diagnosis with positivity (>1.1) of immunoglobulin G and immunoglobulin M (tabl.1). IgM can be detected after one week of illness.

Serological tests for detection of specific R. conorii IgM/IgG using the CLIA method were performed in the Virology Laboratory of the Military Medical Academy-Sofia. VirClia® is the ultimate chemiluminescence solution for the automation of infectious serology in monotest format.

Table 1 Results VirClia® R. conorii IgM/ IgG (positive >1.1)

Results	R. conorii IgM	R. conorii IgG
10.07.2019	negative	1.16
18.07.2019	2.7	6.8
05.08.2019	1.8	5.2

The patient's hospital stay was 9 days. During this period no complications occurred. A favorable response to the clinical symptoms and normalization of laboratory tests were reported. A 14-day antibiotic treatment with doxycycline was performed (started in the clinic and completed at home).

The diagnosis of Marseilles fever was made based on clinical symptoms (fever of several days up to 40 °C, accompanied by chills and the presence of a distinctive maculopapular rash on the body), summer seasonality (the patient fell ill in July), the results of serological tests (seroconversion) and response to antibiotic therapy. At the control examination in early August, the patient did not report complaints and in was in a good overall condition

3. Conclusion

Mediterranean spotted fever is a tick-borne rickettsiosis. Typical symptoms of MSF include fever, maculopapular rash, and a characteristic eschar. Diagnosis is typically based on symptomatology and confirmed through serological assays. Serological diagnostics tests are widely used and molecular techniques have become increasingly available. In the first week after the appearance of symptoms in MSF, the serology for MSF is usually negative. A high reactive titer with diagnostic significance appears in the second week of the disease. In endemic regions, high clinical suspicion must be maintained for patients presenting with fever and undifferentiated rash. Clinical suspicion of MSF is of great importance for the clinicians, in order to promptly initiate antibiotic treatment and avoid the complications of the disease. Doxycycline remains the treatment of choice.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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