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Case Report
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A Mediterranean Spotted Fever Case in a Febrile Trombocytopenia Patient with the Presumptive Diagnosis of Crimean-Congo Haemorragic Fever

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Abstract

Background: Mediterranean Spotted Fever (MSF) is a tick-borne zoonotic infection caused by *Rickettsia conorii*. It is commonly transmitted to humans by dog ticks, *Rhipicephalus sanguineus*. The infection mainly occurs from spring to summer and characterized with fever, headache, myalgia, maculopapuler rash and an inoculation escar at the site of the tick bite. The diagnosis of the disease is difficult due to the asymptomatic clinical features and symptoms, and can lead to misdiagnosis with many disease presented with fever and rash. Laboratory findings are also nonspecific but trombocytopenia, increase in the levels of transaminases, hyponatremia was observed in majority of the cases.

Case Report: In this report we report a ABA case in a 35-year-old male patient, dealt with animal husbandry in an urban province presented with arthralgia, fever, malaise, headache. Patient serum was tested for Crimean-Congo Haemorrhagic Fever (CCHF) by PCR and IFA IgM/G as the clinical features and medical history was compatible with CCHF and negative results were obtained. While patient sera was negative for *Coxiella burnetti* by IFA, IgM 1/96, IgG 1/160 titers was detected for *R.conorii*. The patient received a ten day course of doxycycline, with complete resolution of all symptoms without any complication.

Conclusion: Viral diseases presented with fever and rash, allergic reactions, drug erupsions, typhoid fever, leptospirosis, erlichosis, anaplasmosis and CCHF should be considered in the differential diagnosis and MSF diagnostic testing has to be included in febrile illness with thrombocytopenia, even in the absence of an eschar or a tick bite or rash.

Keywords: Rickettsiosis; Trombocytopenia; Tache noir; Immunflorescent antibody test

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Introduction

Rickettsia is a genus of gram-negative, nonmotile and nonspor-forming bacteria classified into four groups including "*spotted fever*", "*typhus*", "Rickettsia bellii *group*" *and* "Rickettsia canadensis" based on serology [1, 2]. Mediterranean Spotted Fever (MSF) also known as "boutonneuse fever", related with *Rickettsia conorii*. The major vector and potential reservoir is *Rhipicephalus sanguineus*, the brown dog tick [1]. Additionally, *Rh. evertsi*, *Rh. simus*, *Rh. mushamae, Ixodid* ticks and *Rh. bursa* is reported as vectors [1,3]. The incidence of the disease has a seasonal variation related with tick activity mostly occuring between May to September. Also, incidence can be higher due to high temperatures, decrease in rainfall and number of frosty days in the previous year [1].

The disease is characterized with fever, headache, myalgia, maculopapuler rash and typical inoculation escar at the tick-bite site followed by an incubation period of 2-14 days [1]. Symptoms are nonspesific and confused with many diseases characterized with fever and rash, making the diagnosis more difficult. Laboratory findings are also nonspecific but leucopenia, trombocytopenia, increase in transminases, decrease in the serum levels of Na, K, Cl may be seen in most cases [1,4].

The disease is endemic in Mediterranean region including South Europe and North Africa. Cases were also reported from Bulgaria, Ukraine, North and Central Europe, and India [1,2]. In Turkey, the first cases were reported from Thrace region [5]. Although some cases were confirmed by serological tests for Ricketsiosis, many of them were underdiagnosed due to lack of using diagnostic

Figure 1: Tache noir lesion localized on the sculp. Lesion located on the scalp compatible with tache noir.

tests especially in patients outside the area of endemicity or during winter [6]. In this report, we evaluate a MSF case with the presumptive diagnosis of CCHF presented with febrile trombocytopenia but no rash.

Case Presentation

A 35-year old male with fever, headache, generalized myalgia for four days was admitted to a tertier hospital in May 2015. The patient was working in an animal husbandry and living in a rural area located in the central Anatolia. He was febrile (38.5°C) with a pulse rate of 96/min, and blood pressure 140/80 mm/Hg. Rash was not detected and other system examinations were normal. The patient revealed a tick bite prior from the symptoms and removed the tick with his hands and might have been exposed to the excretions of the animals. A black-crusted lesion in a diameter of 2-3 cm surrounded by hyperemic area was observed in the tick-bite area in the sculp (Figure 1). Possible infection sources were evaluated. Additionally, serum sample of patient were send to the Public Health Institution of Turkey, Microbiology Reference Laboratory with the presumptive diagnosis of CCHF. Laboratory tests revealed minimal decrease in hemoglobin (11.9 gr/dl), hematocrite (39.4%), trombocyte (60000/mm^3) and minimal increase in CRP (11.8 mg/dL), sedimentation (25 mm/h). Electrolite levels were normal range except decrease in sodium level (131 mEq/L). Blood samples were also tested for serological markers of viral hepatitis, cytomegalovirus, Epstein-Barr virus, brucellosis, salmonellosis, toxoplazmosis and were all negative. Patient sera was tested for CCHF by RT-PCR (Altona Diagnostics, Germany) and IFA IgM/IgG (Euroimmun, Germany) and were negative. As the patient history revealed rural residence, dog feeding, removal of the dog ticks with his hands and tick bite history and the clinical signs, symptoms of the patient and lesion in the sculp sera was tested with *R. conorii* IFA (Focus Technologies, USA) and *C. burnetii* Phase I-II (Vircell SL, Spain) IFA IgM/IgG. Sample was negative for *C. burnetii* but *R. conorii* IFA were positive for IgM 1/96 and IgG 1/160 titer. Convalescence sera taken after two weeks from the acute sample, *R. Conorii* IFA IgM was 1/384 and IgG 1/640. Detection of *R. conorii* by PCR from escar was not performed as the patient consent was not received.

Evaluation of the case by Raoult et al. [4] MSF diagnostic criteria; revealed a score of 45 with the following parameters of; occurence in spring, exposure to dog ticks, presence of fever, escar, trombocytopenia and four fold increase in the *R. conorii* specific antibody titers between two serum samples (Table 1). The patient was given doxycycline (2x100 mg) empirically. At the third day of the theraphy, fever was decreased, headache, myalgia was resolved and increase in trombocytes (142000/mm^3) were observed and the patient was recovered with complete cure. Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

Table 1: Diagnostic scoring in Mediterranean-Spotted Fever [5].

Diagnostic Criteria	Score
Epidemiological criteria	
Residence/recent travel in endemic region	2
Infection onset between May-November	**2**
Exposure with the dog ticks (confirmed or probable)	**2**
Clinical criteria	
Fever (higher than 39°C)	**5**
Escar (tache noir)	**5**
Maculopapular or purpuric rash	5
Presence of the last two criteria	3
Presence of all three criteria	5
Nonspecific laboratory findings	
Trombocyte < 150 000/mm^3	**1**
ALT or AST >50 U	1
Bacteriological criteria	
Blood culture positivity for *Rickettsia conorii*	25
Skin biopsy positivity for *Rickettsia conorii*	25
Serological criteria (IFA)	
Single serum sample with IgG >1/128	5
Single serum sample with IgG >1/128 and IgM >1/64	**10**
Two serum samples with four fold rise in titer within 2 weeks	**20**

ALT: Alanine transmainase, AST: Aspartate transaminase, IFA: Immun florescent antibody.

Discussion

R. conorii grows in the salivary gland of the ticks, particularly, *Rh. sanguineus* and other *Rhipicephalus* species including *Rh. bursa*, *Rh. evertsi*, *Rh. simus*, *Rh. mushamae* and *Ixodid* species. The bacteria is transmitted to the human during the feeding of the ticks, and as a result of contact with the rodent carcasses while cleaning the weeds [6,7]. Nonspecific clinical, laboratory symptoms along with the lack of escar and rash makes the diagnosis difficult. Although tache noir and rash is characteristics, it may not be observed in all cases [1]. Hyponatremia can be an important diagnostic clue for the physician as it can be the only abnormallity in most cases [8-10]. Two methods are used in the laboratory diagnosis of MSF including direct identification (isolation of the bacteria from samples or identifing bacteria with molecular techniques) and indirect diagnosis (specific IgM and IgG detection) [2]. IFA is considered as reference method with the IgM titer of ≥1/64 is diagnostic. Bacterial DNA can be detected from blood, skin biopsy and from ticks with the molecular methods [2,4]. Gene loci specific to *Rickettsia* genus 17-kDa lipoprotein, citrate synthase, OmpB (outermembrane protein B) and locus specific to spotted fever, OmpA (outer membrane protein A) could be amplified by PCR [11-15]. According to ESCAR study group diagnostic criteria (ESCMID Study Group for Coxiella, Anaplasma, Rickettsia and Bartonella) a score over 25 is diagnostic [16,17].

In our case, patient was admitted to the clinic with the presumptive diagnosis of CCHF. As the testing results were negative for CCHF, the patient was evaluated for other infectious diseases including Ricketsiosis and Q fever because of the history of dog feeding, escar presence and found positive for *R. conorii* antibodies indicating the fact that Rickestiosis could be easily misdiagnosed by CCHF and the prevalence is definitely underestimated due to the lack of testing for Rickettsial diseases in Turkey.

R. conorii IgG seroprevalence in Turkey show variation up to 36.8% [6]. In Turkey, MSF case reports are rare and generally localized from Thrace Region, near the border of Greece where Rickettsiosis is endemic [18-20]. In surveillance studies, *R. conorii* antibodies were detected in North Greece [21] with a frequency of 7.9%. It is estimated that there are at least seven times more cases than reported cases [19,15].

Although *Rhipicephalus sanguineus* is well-adapted to the urban environment, it is specific to the host and fed from human rarely. They fed from human in an environment with the lack of dog host and repellent use of the dogs [17]. *R. conorii* proliferate in almost all organs, especially salivary glands, and allow *Rickettsia* spp. to be transmitted to vertebrate hosts during feeding [6]. In recent years there has been an increase in the number of cases. The increase in the incidence could be explained with increase in the number of ticks, frequency of the contact of the human with infected ticks due to the more often outdoor activities. In addition, climate changes such as temperature increase, rainfall reduction, and a decrease in the number of frosty days in the previous year have also caused changes in tick activity [11].

The MSF case with mortality includes similar epidemiological features, clinical symptoms and laboratory findings with fatal CCHF [7]. In addition, some studies pointed to the co-existence of MSF and CCHF [6]. In a study, of the serum samples collected for CCHF screening, 36.8% were positive for *Rickettsia*, 7.6% for both CCHF and *Rickettsia* IgG [6]. In Albania, of the CCHF suspected cases final diagnosis can be achieved in 82.2% of the cases with the distribution of 38.2% CCHF, 11.7% Hantavirus, 29.4% leptospirosis, and 2.9% Ricketsiosis [9]. It is clear that CCHF should be considered in the differential diagnosis due to the identical epidemiological, clinical and laboratory findings. Lack of escar and tick-bite history may lead to misdiagnosis ve rash may be considered primarily as allergy [7]. Additionally rubella, rubeola, leptospirosis, syphilis, infectious mononucleosis, ehrlichosis, anaplasmosis, allergic reactions, drug eruptions should be kept in mind [7]).

Among ticks removed from patients located in Istanbul half of the ticks were positive for *Rickettsia* spp. by PCR and *R. conorii* was present in the 4% of the *Rh. bursa* [3]. *Rh. sangineus* is not the only vector for *R. conorii* and *Rh. bursa* may be detected [1]. Moreover, *R. conorii* was detected from *Rh. bursa* removed from MSF cases. *R. helvetica* and *R. monacensis*, previously related with MSF-like disease were also detected from *I. ricinus* ticks [10].

Conclusion

In conclusion, it should be considered that Turkey is endemic for tick borne infections due to the geographical location and tick diversity. MSF should be included in the differential diagnosis of fever, headache, myalgia even in the absence of escar and rash during spring and summer, exposure to ticks, dog feeding history. This report is presented at the III. KLIMUD Congress orally (18-22 November 2015, Antalya).

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