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LETTER TO THE EDITOR

A clinical case series of *Rickettsia spp.* from southern Türkiye

Türkiye'nin güneyinden *Rickettsia spp.* klinik olgu serisi

Edanur Yeşil[1], Berfin Özgökçe Özmen[2], Mehtap Akça[1], Özlem Kayabey Koçak[3], Necdet Kuyucu[1]

[1]Mersin University Medical Faculty, Department of Pediatrics, Division of Pediatric Infectious Disease, Mersin, Turkey
[2]Mersin City and Training Hospital, Department of Pediatrics, Division of Pediatric Infectious Disease, [3]Department of Pediatrics, Division of Pediatric Cardiology, Mersin, Turkey

To the Editor,

When fevers and rash occur in children, viral diseases often come to mind. Many possibilities, especially infectious, allergic and rheumatological diseases, are included in the differential diagnosis of skin rashes in children. While questioning the history of contact in infectious etiologies, zoonoses should be considered. In addition, infectious diseases which can be transmitted by vectors such as fly bites and tick bites, as well as animal contacts such as with cats and dogs, should be investigated.

In a review in which epidemiological data related to *Rickettsia* spp. were evaluated, it was determined that 47 *Rickettsia* spp. types with a total of 198 vectors had caused spotted fever group rickettsial (SFGR) infections in 66,133 people since 1906[1]. In the same review, it was stated that the most common 17 species of SFG *Rickettsia* were *Rickettsia felis*, *Rickettsia conorii* and *Rickettsia africae*[1]. In Eurasia, including Turkey, *R. felis* and *R. conorii* were observed in the first two places, *R. slovaca* was in sixth place and *R. aeschlimannii* was in 12th place[1].

Rickettsia rickettsii is the most common rickettsial spotted fever disease, especially in the United States, and it is the causative agent of Rocky Mountain Spotted Fever. Additionally, *Rickettsia conorii*, one of the spotted fever group rickettsiosis diseases, can be transmitted by *Rhipicephalus sanguineus* and *Haemaphysalis* ticks. This is a disease which can cause Mediterranean Spotted Fever (MSF) and it can be seen in North Africa, Kenya, Israel, Pakistan, Southern and Eastern Europe. On the other hand, *Rickettsia slovaca* can cause mild disease and it is usually seen in Europe. It can be transmitted by ticks of the *Dermacentor* genus and can cause tick-borne lymphadenopathy (TIBOLA). *Dermacentor marginatus* and *Dermacentor reticulatis* ticks which transmit the infection are especially found in Europe, North Africa, Turkey and Central Asia[2].

Fever, myalgia and headache are expected in all rickettsiosis spotted fever group diseases. Rash and/or localized eschar (tache noir) usually occurs. *Rickettsia conorii* is seen in the Mediterranean region, Sub-Saharan Africa, Greece, India and Black Sea region countries such as Turkey, Bulgaria, and Ukraine. A rash is present in 99% of cases and tache noir is seen in 73% of cases[3]. However, it can also be seen without a rash.

Rickettsial infections can easily be misdiagnosed as a viral infection as they are rarely seen in pediatric practice. They should absolutely be considered in the presence of maculopapular rashes, especially in endemic areas with a history of tick bites. Early diagnosis and treatment can prevent complications. In this study, *Rickettsia* spp. related infectious disease cases are presented.

This article presents three cases with positive *Rickettsia* spp. serology, who were admitted to the Infectious Disease Department of Mersin City Training and Research Hospital and Mersin University Faculty of Medicine Emergency Departments. Mersin is a city in the south of the

Address for Correspondence: Edanur Yesil, Mersin University Medical Faculty, Department of Pediatrics, Division of Pediatric Infectious Disease, Mersin, Türkiye E-mail: edanuryesil@mersin.edu.tr
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Turkish Republic. The serologies were studied via the indirect immunofluorescent antibody method by transferring the centrifuged serum in a biological material transport container suitable for the cold chain. *Rickettsia* spp. DNA was studied by the real-time polymerase chain reaction method in whole blood with an EDTA tube.

Case-1

A 17-year-old male patient, who had a history of tick bite in a rural area in Germany one week before admission, presented at our pediatric emergency service. On physical examination of the patient, vital signs were normal except for tachycardia. Systemic examinations were normal. However, he had a tache noir rash in the area of the tick bite on the left thigh which had a necrotic center in the middle of the rash (Figure-1). Regarding laboratory parameters, total leukocytes was 14,000/mm3, absolute neutrophils was 13,000/mm3, absolute lymphocytes was 420/mm3, Hb was 13 gr/dl and PLT was 143,000/mm3. Additionally, blood gas, acute phase reactants, and liver function tests were normal. Troponin I was 6,100 ng/L and BNP was 200 pg/mL, both being high. Electrocardiography and echocardiographic evaluations of the case were normal. Cardiac magnetic resonance imaging showed "non-ischemic myocardial fibrotic changes consistent with previous myocarditis". Crimean Congo Hemorrhagic Fever, *Borrelia burgdorferi*, *Francisella tularensis* and *Rickettsia* spp. serology were sent for myocarditis etiology. The patient's serology of *Rickkettsia conorii* IgM was 1/192 titer positive, IgG was negative and all other tests were negative. He was diagnosed with acute Mediterranean Spotted Fever infection. The patient had a positive dramatic response to empirical doxycycline treatment, and the treatment was completed in 7 days. He was discharged after his cardiac enzymes returned to normal.

Figure-1. Case-1, "Tache noir" sign due to *Rickettsia conorii*.

Case-2

A nine-month-old girl presented with fever and maculopapular rash and 0.5 cm lymphadenomegaly in the left axilla two weeks after a tick bite on her left arm (Figure-2). The rash was localized to the arm and no pathology was detected in physical examination or the laboratory findings. *R. slovaca* and *R. aeschlimannii* serologies were detected 1/40 positive. Tularemia, Lyme, *R. conorii* serologies and *Rickettsia* spp. PCR were negative. A rapid improvement was observed in the clinical findings of the patient under empirical ciprofloxacin treatment. Her physical examination was normal, and her rash and fever disappeared during her first week of outpatient control.

Figure-2. Case-2, spotted fever infection after *Rickettsia slovaca* and *Rickettsia aeschlimannii* coinfection.

Case-3

A seven-year-old girl presented with fever reaching 39 degrees which continued for five days, the inability to walk, myalgia, and a rash all over her body (Figure-3). In her physical examination, there were diffuse maculopapular rashes on her body, including the palms of her hands and the soles of her feet, which faded with pressure. Systemic examinations, muscle strength and deep tendon reflexes were normal. In her anamnesis, we learned that the child had scratched a tick from her scalp five days prior. Her laboratory values, which were almost normal, were as follows; total leukocyte: 10,000/mm3, neutrophil:

4,700/mm3, lymphocyte: 4,400/m3, Hb: 11.2 gr/dl, and platelet: 129,000/mm3. Biochemistry and cardiac enzymes were normal. LDH was 444 U/L, ferritin was 220 ng/ml, CRP was 18 mg/L, and sedimentation was 23 mm/hr, all of these being high. The patient's *R. conorii* IgM was 1/768, and IgG was 1/640 titer positive. After doxycycline treatment, her clinical response was dramatically good.

In all of our three cases, the ticks were discarded before hospital admission and could not be sent to the veterinary faculty for species identification. Our first case was a patient living abroad, and the data from Germany, where he lived, were taken into consideration during the epidemiological examination. In the epidemiological research, it was observed that ticks carried the most common Lyme borreliosis pathogen in Germany. Considering the clinical findings of the patient, Lyme disease was not primarily considered because the symptoms occurred shortly after the tick bite incident and Lyme carditis is a condition which is mostly expected to be seen weeks after the tick contact, and it is characterized by cardiac arrhythmias such as atrioventricular block. In the literature, a case of MSF and myocarditis due to *Rickettsia conorii* was reported in a 15-year-old child with G6PD deficiency, and the patient responded dramatically to early treatment, as in our case[4]. In our case, no rash was observed on the body and tache noir was present. In a series on MSF diseases in Eastern Europe, tache noir was seen in 73% of cases[2]. It was stated in two large Eastern European MSF case series that the disease can also be seen without a rash[2].

In the study of Orkun et al. on the infectious agents of *Haemaphysalis*, *Hyalomma*, *Ixodes* and *Rhipicephalus* ticks, it was emphasized that although rare, in tick bite cases in Turkey, *R. aeschlimannii*, *R. slovaca* and *B. burgdorferi* sensu stricto infections should be taken into consideration[5]. With regards to *Rickettsia* spp., when we look at the possibilities of detection by serology, the sensitivity of IFA IgG is 85-100% and its specificity is 99-100%[6]. *Rickettsia* spp. serological cut-off values are not clear, and ≥1/40 or ≥1/960 can be considered significant depending on the agent, and also depending on the endemicity of the region[6]. The *R. slovaca* and *R. aeschlimannii* IgG titers of our patient were found to be 1/40 and it was considered significant because of the factors which are not endemic in our country. In cases of doubt in the diagnosis, seroconversion with elevation of serology titers can be used. In our country, the *R. slovaca* and *R. aeschlimannii* species have been reported in the Central Anatolian region, but not in the southern region of Turkey[7]. In a study by Emiroğlu et al., *R. slovaca* was detected in a three-year-old girl living in Konya who presented with fever, abdominal pain, cervical adenopathy, and eschar in the scalp after tick bite[8]. In a Hungarian article, in approximately half of the cases before 10 years of age, the disease occurred and was classified as tick borne lymphadenopathy (TIBOLA) after a tick bite. The major features of the patients' were a herpes like eschar at the site of the tick bite surrounded by a circular erythema, and ipsilateral lymphadenomegaly[9]. In our second case, there was lymphadenomegaly and rash but no eschar was detected in the physical examination.

Figure-3. Case-3, Mediterranean Spotted Fever due to *Rickettsia conorii* infection.

Rickettsia conorii is the causative agent of MSF from the Spotted Fever group, and it is seen on the Mediterranean coast. In our country, *Rickettsia conorii*

cases have been found in Trakya and Istanbul in the north-west region of Turkey, and more studies on this subject are needed in the Mediterranean region[7]. In 2008, Öztoprak et al. reported a case of MSF from Adana[10].

For the diagnosis of *Rickettsia* spp., in addition to serological examinations, punch biopsy should be taken for molecular and culture studies and DNA should be studied in the tissue in order to determine the causative agent for certain species. Punch biopsy could not be performed in our cases, which is a limitation of this study. At the same time, IFA, with its high sensitivity and specificity, can be used easily in diagnosis as it is both non-invasive and diagnostically guiding[6]. Especially in the presence of fever of unknown origin, maculopapular rash involving the palms of the hands and soles of the feet, and the presence of myalgia or necrotic rash (tache noir) in the tick-infested area, *Rickettsia* spp. should definitely be considered and examined with IFA. With a higher level of suspicion regarding this issue, more cases can be diagnosed and the real epidemiological characteristics of *Rickettsia* spp. can be determined.

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