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Case Report

Mediterranean Spotted Fever and Early Neonatal Sepsis: the Transmission of *Rickettsia conorii* via the Placenta: A Case Report

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Abstract

Mediterranean spotted fever (MSF) is a tick-borne disease caused by *Rickettsia conorii*. The classic clinical triad comprises high fever, an inoculation eschar, and a maculopapular non-pruritic rash. Serological testing is the most frequently used diagnostic method. Treatment involves antibiotics, preferably doxycycline. A two-day-old neonate developed sepsis and a skin rash. There was a high index of suspicion for MSF because the mother and four of her children were diagnosed with MSF in synchronization with the clinical presentation of this neonate. As far as one knows, congenital rickettsia as a cause of early neonatal sepsis has not been reported. However, limited data were reported using animal models. There are several challenges regarding its diagnosis and the selection of proper antibiotics for this age group. This paper discusses the challenges of its diagnosis, treatment, and impact on the neonate, this paper also reviews the literature regarding placental transmission of *Rickettsia conorii*. To the best of our knowledge, this is the first case study reporting that the early neonatal sepsis is caused by *R. conorii* (the Moroccan strain) in Jordan. Physicians caring for pregnant women and neonates living in areas with endemic MSF should consider the possibility of MSF in febrile patients and initiate early appropriate treatment based on a high index of suspicion.

Keywords: Mediterranean spotted fever; *Rickettsia conorii*; Neonate; Placenta; Doxycycline; Jordan

1. Introduction

Mediterranean spotted fever (MSF), also known as Boutonneuse fever, is an acute febrile zoonotic disease caused by *Rickettsia conorii*. It is transmitted to humans through a tick bite of the brown dog, *Rhipicephalus sanguineus*. It is one of the oldest recognized vector-borne infectious diseases (Parola *et al*., 2009). *R. conorii* is an obligate intracellular bacterium that infects vascular endothelial cells. MSF is an endemic disease present in many countries, especially those that surround the Mediterranean Sea. The first case of MSF was reported in 1910 in Tunisia; however, in the past few decades, the incidence of this tick-borne disease has remarkably increased in several countries (Rovery *et al*., 2008), including Jordan.

The clinical course of MSF is usually mild. However, it can be severe in some cases, and therefore requires special attention. The mortality rate of cases diagnosed with MSF has been estimated at approximately 2.5% (Bacellar *et al*., 2003). After an asymptomatic period of approximately one week following the infection, high fever usually arises with flu-like symptoms, and a black eschar at the tick-bite site usually occurs (Raoult and Roux**,** 1997). Between one to seven days (median, four days) following the onset of fever, a generalized maculopapular rash develops. Patients usually recover within ten days without any sequelae. However, severe forms of the disease are associated with different complications, including major neurological manifestations and multi-organ involvement in 5 to 6 % of the cases (Raoult, *et al*., 1983).

Diagnosis is usually based on the clinical symptoms and serology. In addition, common nonspecific laboratory abnormalities in rickettsiosis include mild leukopenia, anemia, and thrombocytopenia. Moreover, hyponatremia, hypoalbuminemia, and hepatic and renal abnormalities may occur, but testing for these non-specific abnormalities is not essential for establishing the diagnosis of MSF (Raoult *et al*., 1997). With respect to serological tests, a comparison of acute- to convalescent-phase serology is required; hence, it is only helpful in retrospect. To the best of the authors' knowledge, this is the first case report discussing the occurrence of early neonatal sepsis in Jordan as a result of the Mediterranean spotted fever (*R. conorii*; the Moroccan strain).

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2. Case Presentation

The patient in the present case study was born in Al-Karak Hospital at a thirty-eight-week gestational age. The mother is twenty-nine years old, gravida 7, para 6. The results of her antenatal screening tests were as follows: rubella-immune; the venereal disease research laboratory test was nonreactive, hepatitis B serum antigen was negative, group B *Streptococcus* (GBS) status was unknown, and her blood type was B+. This pregnancy was uneventful until thirty-seven-week gestation (four days prior to admission) as the mother experienced fever, documented as 39°C when measured orally, together with dizziness, chills, diffuse skin rash, dry cough, and headache.

Her medical and surgical history was not relevant. Her family history revealed that four of her children had similar clinical profiles of high-grade fever, skin rash, and headaches. These children were admitted to the pediatric ward one day prior to her admission.

The general physical examination of the mother yielded normal results except for high-grade fever (39°C). However, the skin examination showed diffuse maculopapular rashes, which started four days prior to admission, and involved the entire body. The obstetric examination showed a thirty-eight-week single viable fetus in vertex presentation, with adequate amniotic fluid, anterior placenta, and no obvious gross congenital anomaly. The mother's other physical examinations were normal. Her basic investigations haven't revealed any abnormalities except for ESR which was 110 mm/hr.

The mother was admitted to the obstetrics ward with a chest infection, and was administered antibiotics (Ceftriaxone and Azithromycin). After three days of treatment, she was stable and afebrile. The non-stress test showed a normal reactive fetus. Induction of labor was initiated. Intrapartum prophylaxis for group B streptococcus was started using 2 g of ampicillin as the loading dose followed by 1 g every eight hours. The membranes were ruptured eight hours before delivery, and the liquor was clear. All stages of labour were uneventful. The newborn's APGAR score was 7/8, weight was 3 kg, and head circumference was 35 cm. The routine neonatal care was provided, and no specific resuscitation procedures were needed. Therefore, the newborn was discharged with his mother twelve hours after delivery following the routine postnatal examination.

The newborn was readmitted to hospital on day two of life with a history of high-grade fever associated with a maculopapular skin rash and diarrhea. In addition, he was hypoactive with poor feeding, and had been lethargic for twelve hours prior to admission. The general physical examination showed an ill-looking baby who was hypoactive but conscious and not distressed. The vital signs were as follows: temperature 39°C measured rectally; heart rate 140 bpm; Respiratory rate 60; O_2 saturation 96% in room air; blood pressure normal; and capillary refill time within two seconds. The newborn was hypoactive with weak crying, and jaundiced with acro-cyanosis, but no central cyanosis or pallor. The skin examination showed maculopapular skin rashes over the antecubital area, groin, and anterior aspect of the neck, which diffused later to involve the entire body. His neurological examination showed poor motor reflexes, poor sucking reflexes, and poor response to tactile stimulation, the anterior fontanelle was open and not bulging. All suture lines were normal, with no signs of birth trauma. There were no dysmorphic features. His cardiovascular, respiratory, and genitourinary examination results were normal.

The newborn was admitted for treatment of early neonatal sepsis. His initial septic work-up was negative for the usual-early neonatal sepsis-microorganisms (Table 1), the baby was administered ampicillin and gentamicin. A few hours after admission, he developed more diffuse skin rashes. The serological test results for his brother and sisters came back strongly positive for rickettsia (Table 2). Because the mother's serological test results were equivocally positive on day ten following the start of her symptoms, it was suspected that the newborn had congenital rickettsia. Therefore, he was administered doxycycline plus imipenem and vancomycin. His mother's serology for rickettsia was retested on day fourteen after the start of her symptoms, which again showed strongly positive results. The newborn's serological test results on days two and five after admission were negative, and on day ten they changed to weakly positive. The test used in this study was Vircell *Rickettsia conorii* plate: 96-wells plate coated with *R. conorii* antigen, strain Moroccan (ATCC VR-141) (Vircell S.L., Granada, Spain). The identification of the *Rickettsia* serotype (using the American Type Culture Collection VER-141) proved that it was *R. conorii* (the Moroccan strain) in all the positive cases of newborn's family. The newborn status improved forty-eight hours after admission. Fever subsided, skin rashes started to disappear, and his activities (including motor and sucking reflexes) significantly improved. He restarted feeding, and achieved full feeding on day nine of admission. The results of his laboratory examination for rickettsia-related complications were normal.

Table 1. Diagnostic data of the newborn

Laboratory	CBC : WBC, 15.5×10^3/µL	Hb, 18.5 g/dl
	Plt, 267×10^9/L	Mo, 8%
	Gr, 59	Lymph, 33%
	CSF: WBC, 2HPF; RBC, abundant traumatic tab; sugar and protein were normal.	
	Acute phase reactant: CRP: positive	
Cultures	No growth for blood, urine and CSF cultures	
Radiology	Brain CT: hyperdense tiny area seen in the left hemi-cerebellum may represent hemorrhage.	
	CXR: Normal	

CBC, complete blood count; RBC, red blood cell count; Hb, hemoglobin; WBC, white blood cell count; Plt, platelet; Mo, monocyte; Gr, granulocyte; Lymph, lymphocyte; CXR , chest X-ray; HPF, high-power field;

Table 2. Diagnostic Data of the Mother and the Siblings

Patient	Age (Years)	Presentation	LFT*	ESR*	Sodium*	Serology day 1	Serology day 7	Serology day 14
The mother	29	Fever, Skin rash	Normal	Elevated	decreased	Negative	Equivocal positive	Strongly Positive
Sibling 1	7	Fever, Skin rash	Slightly elevated	Elevated	decreased	Strongly Positive	Strongly Positive	Strongly Positive
Sibling 2	6	Fever, Skin rash	Slightly elevated	Elevated	decreased	Strongly Positive	Strongly Positive	Strongly Positive
Sibling 3	5	Fever, Skin rash	Slightly elevated	Elevated	decreased	Strongly Positive	Strongly Positive	Strongly Positive
Sibling 4	3	Fever, Skin rash	Slightly elevated	Elevated	decreased	Strongly Positive	Strongly Positive	Strongly Positive
The newborn		Fever, Skin rash	Slightly elevated	Elevated	Normal	Negative	Negative	Weakly positive

*LFT (liver function test), ESR (erythrocyte sedimentation rate) and sodium are positive tests usually been abnormal in Rickettsia infections

3. Discussion

3.1. Diagnosis and Work-up

The case presented here demonstrates the difficulties associated with the diagnosis and treatment of congenital MSF. The authors searched the medical literature in the PubMed database using the key words vertical transmission and trans-placental transmission, which were cross-matched with *R. conorii*, MSF, Boutonneuse fever, and rickettsiosis. Relevant references cited in the selected articles were also reviewed. During this search, we found very limited data describing congenital rickettsiosis in animal models. In consistence with the findings of these small publications, no vertical transmission was demonstrated. It has been demonstrated that rickettsiosis caused by *R. conorii* and *R. ricketsii* during pregnancy presented no risk of vertical transfer of these pathogens to offspring (Stallings, 2001**)**. However, the possibility of trans-placental transmission in other groups of pathogens, for example, *R. prowazekii*, transmitted by *P. humanus* in guinea pigs, has been demonstrated (Kurganova and Klimchuk, 1996). This small published data on animal models regarding congenital rickettsiosis due to *R. conorii* does not provide sufficient evidence supporting that the trans-placental transmission does not occur. Furthermore, this problem of trans-placental transmission of *R. conorii* needs to be additionally investigated in mammals, which can serve as reservoir species (Jasik *et al*., 2015).

Because congenital *R. conorii* infections are not well-reported for the neonatal age group, the diagnosis of MSF for this patient was not straightforward. The ultimate diagnosis was confirmed using his maternal history, family history, clinical presentation, and the epidemiological data of the disease in the study area.

3.2. Epidemiological Data

During the past few years, many cases of high-grade fever, skin rashes, and hyponatremia were observed. However, a black crusted eschar (tache noir), which is considered to be the site of the tick bite, was absent in these cases. Moreover, some of these cases were severe, and led to the development of thrombocytopenia and rapid multi-organ failure, resulting in a high mortality rate. Although comprehensive laboratory tests including polymerase chain reaction assays of several viruses were performed, no clear diagnosis could be made at the time. In the early summer of 2013, a small outbreak of cases occurred among patients all living in the same rural area and having close contacts with animals. Therefore, serological tests were performed for several diseases, including *Rickettsia*. In June 2013, the first case of *Rickettsia* was diagnosed at the formerly-mentioned hospital in Jordan. Since then, the same diagnosis has been given for each case presented with a high-grade fever and skin rash. In 2017, the authors published a retrospective observational study describing the epidemiological patterns of Mediterranean spotted fever (MSF), as well as its treatment and impact on children in southern Jordan (Nafi *et al*., 2017). Over a thirty-month period (from June 2013 to December 2015), we recorded fifty-five pediatric cases of MSF in that southern province, with an incidence rate of 7.9 cases per 100,000 inhabitants. MSF affected 89% of those individuals during summer. 74.5% of those patients were living in a rural area with tent housing, and 100% of them had contact with animals. All cases had fever, and 94.5% had a skin rash. Serological tests were positive in 87.2% of the cases. The incidence rate in Jordan is higher than that in Spain, but is lower than that in Bulgaria (Nafi *et al*., 2017).

The strong epidemiological link between this newborn and *R. conorii* was the history of his siblings and his mother, who were diagnosed and treated with *R. conorii* a few days before his birth. The diagnosis of *R. conorii* was confirmed by serological testing, and *R. conorii* (the Moroccan strain) was present in all the positive cases of his family.

3.3. Family History and Clinical Presentation

The clinical presentation of MSF in Jordan is similar to that in Europe (Nafi *et al*., 2017). Patients usually have a classic triad of fever and chills, severe headaches, and/or myalgia, in addition to a typical rash (Font-Creus *et al*., 1985; Raoult *et al*., 1986). The presence of a black crusted eschar (tache noir), which is considered to be the site of the tick bite, is very rare in MSF patients in Jordan (Nafi *et al*., 2017; Font-Creus *et al*., 1985; Raoult *et al*., 1986; Mumcuoglu and Keysary, 2002; Wolach *et al*., 1989).

The newborn of this study had three sisters and one brother who were admitted to the pediatric ward with the classic triad symptoms of MSF (fever and chills, severe headache, and myalgia). They also had a typical macular erythematous rash which appeared three days after the abrupt onset of fever. A black crusted eschar was absent in all the siblings. Based on the epidemiological data of the family and their clinical presentation, they were all admitted for suspicion of MSF, which was confirmed by the immunofluorescence assay on the same day of admission and by serotype testing on day seven after admission.

Although the clinical presentation of the mother at the disease onset was ambiguous, her diagnosis was established based on MSF findings in other family members and the epidemiological data of the family. Therefore, the mother was retested for *R. conorii* infection using the immunofluorescence assay on day two after the admission of her newborn (or day ten of her own disease onset). Results showed equivocal results initially, but they were strongly positive fourteen days after the disease onset, confirming that the mother had the Moroccan strain of *R. conorii*.

The newborn had a clinical profile similar to that of his family members, who were all (including the mother) confirmed to have MSF due to the infection with *R. conorii*. His initial septic work-up results were negative for the usual microorganisms. Because positive serology often requires waiting for convalescent titers, the decision was made to treat the patient for MSF due to *R. conorii* infection on day two of his admission. Nevertheless, diffuse skin rashes started to appear despite the fact that his mother's initial serological test results were equivocal. Most importantly, the clinical profile of *R. conorii* infection during early neonatal sepsis was not adequately studied, and there is very limited information in the published literature regarding its clinical presentation in the neonatal age group. Moreover, the early diagnosis and treatment of the disease are essential for an uncomplicated recovery. Because there are no convenient tests to diagnose the disease during its early course (Mumcuoglu and Keysary, 2002), the authors had to rely on a high index of suspicion despite the negative initial serology. As demonstrated in the mother's case, positive serology does require waiting for convalescent titers (Bentov *et al*., 2003).

3.4. Serologic Tests

Although the serologic tests are the most widely-available diagnostic tools for spotted fever, they are less than optimal for the diagnosis of rickettsia diseases' acute phases (Paddock et al., 1989). Moreover, the underdiagnosis of the fatal spotted fever may be attributed to the nonspecific clinical features and the insensitive acute-phase serologic studies (Weinberger *et al*., 2008). Serologic tests for the *R. conorii* infection in the newborn on day two of his admission (day ten of his mother's illness) yielded negative results (for both immunoglobulins IgM and IgG). On day ten of his illness, IgG results remained negative, and the IgM results were weakly positive. This may be attributed to the immature immune responses of neonates, or the fact that the mother was already treated with azithromycin, one of the alternative drugs for treating *R. conorii* infections during pregnancy (Bentov *et al*., 2003).

The importance of an early diagnosis and initiation of treatment in clinically-significant cases is reinforced by the fact that severe complications may develop, and the disease may unexpectedly take a rapid, fatal course. Fatalities have been reported in 1.4-5.6% of the hospitalized patients in Israel, France, and Portugal (Raoult *et al*., 1986; Mumcuoglu and Keysary, 2002; Aharonowitz *et al*., 1999; Botelho *et al*., 2012; Lucio-Villegas *et al*., 1990). Based on this, and due to the high index of suspicion, the diagnosis of MSF was made.

3.5. Treatment

In regions where MSF, caused by the *R. conorii* infection, is epidemic, an antibiotic therapy helps prevent the severe progression of the disease, and mortality (Lucio-Villegas *et al*., 1990; Anton *et al*., 2015). Although the clinical presentations and serological findings at the onset of disease in the patient were ambiguous, early treatment is considered to be essential for an uncomplicated recovery. Fatal outcomes in this region have been reported of previously- healthy children because the appropriate and timely antimicrobial drug-treatment was not administered in 2013 (Nafi *et al.*, 2017). Therefore, the administration of doxycycline pending the results of initial blood and CSF cultures, later showed no growth of the usual microorganism suspected during early neonatal sepsis.

The classic antibiotic therapy consists of tetracycline or chloramphenicol. The use of

Chloramphenicol in developed countries is limited due to its bone marrow toxicity (Bentov *et al*., 2003; Anton *et al*., 2015; Woodward 1991; Brouqui *et al*., 2007; Shaked *et al*., 1989). The first line of antibiotics for treating rickettsial diseases are tetracycline's (Bentov *et al*., 2003; Maurin and Raoult, 1997; Herbert *et al*., 1982). Doxycycline has replaced chloramphenicol as the drug of choice for this indication in children because of the recommendations of the American Academy of Pediatrics in 1991. Doxycycline has also become a common alternative for tetracycline, especially for children, because of its prolonged half-life enabling single or double daily doses, and because it is less prone to causing dental staining (Yagupsky *et al.*, 1987**)**. In 2015, Todd *et al* published a study indicating that children who received short-term courses of doxycycline at ages younger than eight years did not develop dental staining, enamel hypoplasia, or tooth color differences. That study provided the largest sample size and best evidence to date that short courses of doxycycline (such as those used to treat rickettsial diseases) do not cause dental staining when administered to children younger than eight years of age.

Both *in vitro* and *in vivo* studies have shown that doxycycline is highly efficacious for treating rickettsiosis (Anton *et al*., 2015). Even short-term treatments with doxycycline are highly effective (Anton *et al*., 2015; Bella-Cueto *et al*., 1987) Doxycycline is the gold standard treatment for MSF, and it is the most commonly used treatment for this disease (Anton *et al*., 2015). Clinical studies have demonstrated that doxycycline shortens the course of MSF and induces a rapid remission of symptoms (Botelho *et al*., 2012; Lucio-Villegas *et al*., 1990; Anton *et*

al., 2015). Recent evidence suggests that despite the potential side effects, doxycycline should be considered the drug of choice for children of all ages in whom a rickettsial disease is considered during the differential diagnosis of illness (Purvis and Edwards, 2000). Despite this, a national survey conducted in 2012 showed that only 35% of clinicians correctly chose doxycycline as the treatment of choice for suspected MSF in children younger than eight years old. The centers for disease control highlighted these issues in 2015. Doctors often avoid prescribing doxycycline to young children because of the warning that tooth staining may occur when used for children younger than eight years old. This misconception about the use of doxycycline for children prevented them from receiving a lifesaving treatment.

Based on previous evidence, doxycycline was administered to the patient of this study because it is believed to be the most effective treatment for all rickettsial diseases, and because previous studies have shown that other antibiotics are less effective, and are associated with a higher number of deaths (case fatality rate). The patient was discharged on day ten of admission, and was doing well, with full feedings achieved, afebrile status, and no skin rashes. He had regular follow-up examinations until he was eight months old, which showed that all of his growth parameters were within the normal ranges, including weight, body length, head circumference, hearing test, ophthalmic examination, and laboratory evaluations.

4. Conclusions

This case underscores the difficulties involved in establishing the diagnosis of MSF during pregnancy and the neonatal period. The absence of both, eschar and positive serology, which usually necessitates awaiting convalescent titers, is an obstacle to a correct diagnosis. For this reason, physicians caring for pregnant women and neonates living in areas with endemic MSF should consider the possibility of MSF in febrile patients and initiate early appropriate treatments based on a high index of suspicion. The suspicion could be attributed to the clinical presentation and the epidemiological data of the patient despite the negative initial serology. Doxycycline is the gold standard and most commonly-used treatment for MSF.

Based on the case of this study, R. *conorii* can assumingly penetrate the placental barrier and lead to the infection of the fetus and the newborn; this may be subject to evolutionary fitness. It has been shown through the review of literature that the mechanism for this pathogen to cross the placental barrier has been discussed in few model studies, but there is much ambiguity. For this reason, the issue of vertical transmission requires further attention.

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