Scientific Research Publishing

Journal of Biosciences and Medicines, 2023, 11, 143-149
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

The Role of Mediterranean Spotted Fever in the Spectrum of Pediatric Fever with Rashes

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How to cite this paper: Skenderi, E., Sulovari, A., Kuli-Lito, G., Shkembi, A., Shehu, A. and Babo, A. (2023) The Role of Mediterranean Spotted Fever in the Spectrum of Pediatric Fever with Rashes. *Journal of Biosciences and Medicines*, **11**, 143-149.
https://doi.org/10.4236/jbm.2023.111014

Received: December 16, 2022
Accepted: January 25, 2023
Published: January 28, 2023

Abstract

When febrile illnesses develop a rash in children, parents are very concerned about a serious disease. Many rashes associated with fever are caused by infectious diseases. Rashes are generally nonspecific and play a supportive role in differential diagnosis, but for some diseases, the appearance of the rash is essential in making a diagnosis. Here is presented the case of a 4-year-old boy with high fever, headache, abdominal pain, vomiting, diarrhea, and a generalized maculo-papular rash including palms and soles. On physical examination were found a black eschar, cervical lymphadenopathy, and hepatosplenomegaly. Laboratory findings resulted in moderate leukocytosis and moderate involvement of the liver and renal function. Based on this finding, a diagnosis of Mediterranean Spotted Fever was performed. The child recovered after medication with azithromycin. Because there is no reliable test that can confirm MSF in its early stages, the diagnosis is commonly made on the basis of clinical findings, so a high index of suspicion should be maintained while evaluating a child with fever and rash.

Keywords

Fever, Rash, Eschar, Children, Rickettsiosis, Mediterranean Spotted Fever

1. Introduction

Mediterranean Spotted Fever (MSF), a tick-borne disease, is caused by *Rickettsia conorii subspecies conorii* (*R. conorii*) which is an organism that is endemic in the Mediterranean region. MSF was first reported and described clinically in Tunisia in 1910 by Conor and Burch and soon after was reported in other regions around the Mediterranean basin [1]. *R. conorii* has been identified as the

causing agent of MSF and was first described in 1932 by Brumpt [2]. *Rickettsia conorii* is a small, obligate, intracellular, gram-negative, rod-shaped bacteria ranging from 0.3 - 2.0 μm, belonging to the Spotted Fever Group (SFG) of the genus *Rickettsia* in the family *Rickettsiaceae.* The SFG *Rickettsiae* is natural parasites of certain arthropods. Humans are accidental hosts. *R. conorii* is transmitted to humans by the brown dog tick *Rhipicephalus sanguineous* which is the most common tick species along the Mediterranean coast and in several other European countries.

After inoculation by a tick bite, *R conorii* invades and proliferates in the endothelial cells of small vessels, causing endothelial injury and tissue necrosis. The incubation time of MSF is typically 5 to 7 days after the infecting tick bite, which is typically painless and often goes unnoticed [3]. Approximately, one-third of patients give a history of a tick bite, and most of them report having had contact with a dog, live, or have a history of travel to an endemic area. MSF is characterized by the triad of: fever, maculo-papular rash, and an eschar at the site of the tick bite. Fever is present in almost all patients after the incubation period. Other symptoms that appear early in the course of the disease are: headache, arthralgias, myalgias, local lymphadenopathy, hepatomegaly, splenomegaly, and gastrointestinal symptoms. The majority of patients develop a sparse macular rash which becomes maculo-papular and generalized involving the palms and soles and sparing the face. The rash appears 2 - 3 days after the onset of fever, in rare cases, it is absent and is called "spotless fever" [4] [5]. The characteristic eschar "tache noire" has a variable frequency, presenting in more than 60% of cases. In adults, it is usually located on the trunk and the lower and upper limbs, whereas in children, it is usually found on the head, neck, and auricular region [6].

Although MSF was considered a benign disease, severe sequela has been reported and includes Guillian-Barré syndrome, polyneuropathy, altered mental status, hepatomegaly, acute renal failure, thrombocytopenia, hypoxemia, hemophagocytic lymphohistiocytosis, and death [7] [8]. There is no test that can reliably confirm MSF in its early stages, so the diagnosis is commonly made on the basis of clinical findings. On serologic testing, the antibody titer in serum is increased only 2 weeks after the infection and reaches its peak level after 4 weeks. Afterward, the Immunoglobulin M (IgM) level decreases and the Immunoglobulin G (IgG) level remains high for several months. Titers of 1:64 or greater are diagnostic [9]. The course of Mediterranean Spotted Fever (MSF) can be shortened with appropriate antibiotics. Doxycycline is considered the first-line antibiotic of choice for MSF. Clinical response is typically observed after 2 - 4 days of first-line therapy, as noted by the decrease in fever and the slow resolution of the maculopapular rash. Clarithromycin and azithromycin are an acceptable alternative to doxycycline for MSF [10]. Single-dose azithromycin can be used for prophylaxis of MSF following a tick bite in an endemic area.

Here is reported the case of a child with Mediterranean Spotted Fever, to high-

light the role of MSF in the spectrum of childhood fever with rashes.

2. Case Report

A 4-year-old boy was admitted at the University Hospital Center "Mother Teresa" of Tirana, Albania in late summer with a history of 5 days high-grade fever of 38.5˚C - 39.5˚C, maculopapular rash (appeared on the third day of fever), headache, chills, vomiting, loose stool (5 - 6 times a day), abdominal pain. He was treated with broad-spectrum antibiotics (ceftriaxone) by the local clinic, but the fever persisted and the general condition was deteriorating.

The child lived with his parents in the city of Durres, which is located in the costal area of Albania. All the family members were healthy and he had been healthy too till then. Vaccination was performed according to the age of the child. The family did not keep domestic animals at home and consumed safe food; however, the child was reported to have played with the neighborhood dog.

On physical examination, the child appeared ill, with high fever of 39.5˚C. Although he was irritated, neither stiff neck nor other neurological anomalies were observed. Sclera was slightly injected, and pharyngeal injection and cervical lymphadenopathy were observed. A maculopapular rash was spread over the trunk, and extremities including palms and soles too, accompanied by slightly swollen hands and feet (**Figure 1**). On the posterior area of the neck at the hair line border was found a black eschar. There was observed elevated respiratory rate of 35 - 40 breaths/min, and elevated heart rate of 120 beats/min. The abdomen was soft, not distended, bowl sounds were present, and liver and spleen were slightly palpable.

Laboratory examination revealed: WBC 16,100 cells/mm^3 (41% neutrophils, 52% lymphocytes), RBC 3,280,000 cells/mm^3, mild anemia Hemoglobin level 9.7 g/dl, Hematocrit value 32%, Platelet count (PLT) 160,000 cells/mm^3, Erythrocyte sedimentation rate 22 mm/h (<15 mm/h), elevated Aspartate aminotransferase 96 U/L (21 - 44 U/L), elevated Alanin aminotransferase 113 U/L (9 - 25 U/L), elevated Blood Urea Nitrogen (BUN) 45.2 mg/dL (10.9 - 36 mg/dL), elevated Creatinine 0.63 mg/dL (0.38 - 0.54 mg/dL), serum Total Protein level 5.2 g/dL (5.6 - 7.5 g/dL), Albumin 3.3 g/dL (3.8 - 5.4 g/dL), elevated C reactive protein 2.7 mg/dL (<0.5 mg/dL), normal Fibrinogen activity 315 mg/dL (160 - 390 mg/dL), normal Ferritin value 56 ng/mL (13.7 - 79.8 ng/mL) (**Table 1**).

Radiologic examination of thorax and abdomen revealed peribronchial changes and slightly increased liver and spleen. Serologic examination for Salmonellosis, Brucellosis, HIV, EBV, CMV, Hepatitis A, and COVID-19 were negative. Cultures of blood, urine and feces resulted in no bacterial growth. The Weil-Felix agglutination test resulted in 1:80. According to the clinical findings and the Weil-Felix test the diagnosis of Mediterranean Spotted Fever was performed. The child was treated with Azithromycin. Fever subsided on the the second day of treatment, rash gradually faded and the child was feeling well and playful. The Weil-Felix agglutination test performed 2 weeks later resulted negative and the radiologic examination of the thorax and abdomen were both normal.

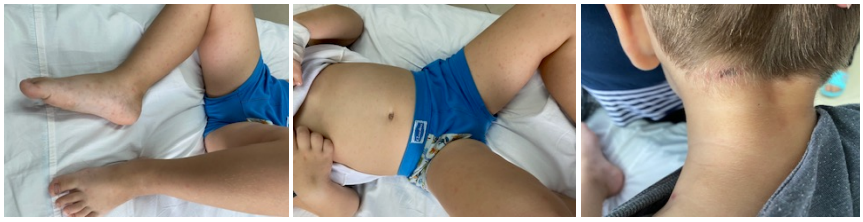

Figure 1. The maculopapular rash and the eschar.

Table 1. Laboratory examinations values.

WBC	16,100 cells/mm^3
RBC	3,280,000 cells/mm^3
Hemoglobin	9.7 g/dl
Hematocrit	32%
PLT	160,000 cells/mm^3
ESR	22 mm/h (<15 mm/h)
ALT	113 U/L (9 - 25 U/L)
AST	96 U/L (21 - 44 U/L)
BUN	45.2 mg/dL (10.9 - 36 mg/dL)
Creatinine	0.63 mg/dL (0.38 - 0.54 mg/dL)
Total protein	5.2 g/dL (5.6 - 7.5 g/dL)
Albumin	3.3 g/dL (3.8 - 5.4 g/dL)
Weil-Felix Test	1:80
CRP	2.7 mg/dL (<0.5 mg/dL)
Fibrinogen	315 mg/dL (160 - 390 mg/dL)
Ferritin	56 ng/mL (13.7 - 79.8 ng/mL)

3. Discussion

When a child with fever develops rash, parents are very concerned of a serious disease. In fact, many rashes associated with fever, are caused by infectious diseases. A skin rash is a symptom that appears during the course of a systemic or localized disease [11]. Rashes are generally nonspecific and play supportive role in differential diagnosis, but for some diseases the appearance of the rash is essential in making a diagnosis. The location, pattern, rate of emergency, accompanying pruritus, association between the rash and fever, the morphology of the rash, seasonal occurrence, all play supporting roles in the diagnosis [12]. Ongoing researches have revealed good correlations with morphology and etiology. So erythematous-vesicular pattern was exclusive to viral infections, pustular and papular pattern pattern were found in drug reactions. Whereas macular and maculopapular patterns were distributed among various diseases. Maculopapular rash is the most common type of rash in a viral infection, but can occur with immune-mediated diseases, drug reactions, and systemic bacterial infections [13] [14]. Systemic rashes mostly appear centrally rather than peripherally. For clini-

cal diagnosis of diseases accompanied by fever with rash, a careful history must be taken, including recent travel, contact with animals, drugs, and exposure to natural environments [15].

The child in the presenting case lived in Durres, the largest city on the costal area of Albania, which is characterized by hot-summer mediterranean climate, making it a perfect environment for the survivor of the Rickettsia tick (brown dog tick *Rhipicephalus sanguineus*). The contact of the child with dogs was confirmed by his parents.

The onset of the disease was sudden with fever up to 39˚C, headache, chills, myalgias, vomiting, diarrhea and abdominal pain. Fever is the first symptom in MSF.It is present in all patients and ranges from moderate degree 38˚C to high degree >40˚C. Symptoms of headache, myalgias and arthralgias are more consistent in adults but are referred in children as well. Whereas gastrointestinal symptoms (abdominal pain, vomiting, diarrhea) are reported more frequent in children [4] [6] [16]. This prevalence of gastrointestinal symptoms in children is suggested to be caused by the physiological, anatomical features and special reactivity of children's gastrointestinal system, which are present in other diseases of childhood too.

A maculo-papular rash over the trunk, limbs, palms and soles, but sparing the face, developed in the third day of fever. The rash, which is one of the main symptoms of MSF is typically maculopapular, unevenly distributed (scarce or more abundant), unequally in size, envolving palms and soles, at times progress to petechial or haemorrhagic which are linked to more severe forms of the diseases.

The presence of the characteristic eschar, "tache noire", on the posterior area of the neck at the hair line completed the triad of MSF. The eschar is one of the main clinical findings of MSF, but it is not present in all cases, it is observed in approximately 60% of cases. In children it is found on the head, neck, at the auricular region, whereas in adults it is usually located on the trunk, and upper and lower limbs [6] [17]. Regional (cervical) lymphadenopathy accompanied by hepatomegaly, which are present in the reported case, are found in greater frequency in children than in adults.

Mild hepatitis (manifested by increase of liver enzymes), and renal involvement (mildly elevated blood urea nitrogen and creatinine), together with the upper discussed symptoms and signs, made possible the classification of the case as a moderate form of MSF. There is no reliable test to diagnose rickettsia infection in its early stages, so diagnosis is made on the basis of clinical features, which are generally nonspecific and easily confused with other conditions as serious bacterial infection, menigococcemia, sepsis and bacterial meningitis.

The Weil-Felix agglutination test used for the diagnosis of rickettsial infections, lacks high sensitivity and specificity, but serves as an inexpensive screening test. Weil-Felix titers of more than 1:80 are considered significant for a presumptive diagnosis of rickettsiosis [18]. The gold treatment for MSF is doxycyc-

line, however, in children under eight years of age, there is concern regarding possible permanent tooth discoloration [19]. The child in the presented case (4 years old) was successfully treated with Azithromycin.

Albania is considered an endemic country, and the spotted fever has been reported from the coastal region, western lowland, and middle region. However, as in many endemic countries, the true incidence of MSF is unknown because mild infections are common, and are under-diagnosed or under-reported.

4. Conclusion

MSF cases are on the increase all over the world. Children suffer from milder forms of the disease; however, severe and malignant forms which seriously affect the entire organism have been reported. Because there is no reliable test that can confirm MSF in its early stages, the diagnosis is commonly made on the basis of clinical findings. The course of MSF can be shortened and complications avoided with appropriate antibiotics, so a high index of suspicion should be maintained while evaluating a child with fever and rash.

Acknowledgements

We thank all the medical staff of the General Pediatric Ward for their constant support!

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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