Short Communication

Murine Typhus with Marked Thrombocytopenia in a Child in Northern Greece and Literature Review

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SUMMARY: We report a case of murine typhus in a 4-year-old boy living in northern Greece. Although the illness started with mild symptoms, a maculopapular rash appeared by the end of the first week of illness followed by marked thrombocytopenia. The detection of IgM antibodies against *Rickettsia typhi* in the patient’s blood and a positive polymerase chain reaction result combined with sequencing confirmed the diagnosis of infection by *Rickettsia typhi*. Clinicians in northern Greece should be aware of the disease, even in cases presenting with no specific initial symptoms.

Murine typhus, also known as endemic typhus, is a flea-borne disease with a worldwide distribution and is caused by *Rickettsia typhi*. Murine typhus is primarily transmitted by the rat flea, *Xenopsylla cheopis*, while the cat flea (*Ctenocephalides felis*) and the mouse flea (*Lep-topsyllia segnis*) serve as additional vectors. Humans are infected by inoculation of infective flea feces in bite wounds, and the incubation period is 7–14 days. Murine typhus is usually a benign illness characterized by fever, headache, and macular or maculopapular rash; other nonspecific symptoms and signs may also be present. Children exhibit several different characteristics, which mainly include gastrointestinal symptoms, such as abdominal pain, vomiting, and diarrhea (1,2). Owing to the non-specific symptoms, the clinical diagnosis and laboratory confirmation of murine typhus is challenging and may be delayed, leading to underdiagnosis of the disease and unclear incidence.

In August 2016, a fully immunized 4-year-old boy who lived in a village in Kavala Prefecture, northern Greece, was admitted to the Pediatric Clinic of Kavala General Hospital with fever (38.8°C), symptoms of upper respiratory tract infection, and intermittent abdominal pain (day 1 of clinical presentation). His medical history included mild psychomotor retardation. The patient was dismissed and the parents were advised to have the patient re-examined if the fever persisted or his medical condition deteriorated. On day 3, the child was admitted again to the hospital with a higher fever (39.9°C), anorexia, and abdominal pain accompanied by vomiting and diarrhea (2–3 episodes daily).

Hematological and biochemical testing showed 5,050 white blood cells/μl with 68.9% neutrophils (normal range 42.2–75.2%), a C-reactive protein level of 2.5 mg/

dl (normal value < 0.5 mg/dl), low blood sodium level (129 mmol/l, normal range 136–145 mmol/l), and slightly elevated aspartate aminotransferase level (43 U/l, normal range 15–37 U/l). His platelet count, renal function, and abdominal ultrasound examination were normal. Cefuroxime was prescribed (30 mg/kg/24 h in 2 doses) and the patient was sent home.

On day 7, the patient returned to the hospital with a high fever, chills, myalgia, severe headache, and maculopapular rash. The patient still had abdominal pain and 2–3 episodes of vomiting and diarrhea daily and had been unable to accept oral medical treatment. The rash began as a maculopapular eruption on the trunk, with no petechial component, although in the following days it spread peripherally, sparing the palms and soles. On physical examination, no lymphadenopathy was present, but a neurological examination showed muscle weakness. However, examination of the patient was difficult owing to his mild psychomotor retardation. The patient was admitted to the Pediatric Clinic for further evaluation and treatment.

The main laboratory findings were as follows: white blood cells, 6,580/μl with 77.3% neutrophils; hemoglobin, 12.9 g/dl, platelets, 98,000/μl; C-reactive protein, 5.8 mg/dl; sodium, 134 mmol/l; lactate dehydrogenase, 459 U/l (normal range 85–227 U/l); aspartate aminotransferase, 56 U/l; and alanine aminotransferase level, international normalized ratio, and activated partial thromboplastin at normal levels. No abnormalities were seen on chest radiography, and a blood culture was negative for common pathogens.

Empirical treatment was started with intravenous (IV) cefuroxime (90 mg/kg daily in 3 doses). On day 9 (3rd day of hospitalization), the patient still had a high fever, headache, and a widespread distinct maculopapular rash. New laboratory testing showed a further decrease in his platelet count (72,000/μl) and hemoglobin (11.3 g/dl) and an increase in C-reactive protein (8.7 mg/dl). Owing to the clinical and laboratory deterioration, the IV treatment was changed to ceftriaxone (100 mg/kg daily in 1 dose), because of concern about a bacterial infection resistant to cefuroxime.

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However, the characteristic triad of fever, headache, and rash, accompanied by a normal white blood cell count with a left shift, marked thrombocytopenia, hyponatremia at the onset, and elevated aspartate aminotransferase raised the clinical suspicion of rickettsial disease. The parents were repeatedly asked about a history of arthropod bites, and although they initially did not mention any bite, they finally recalled several flea bites 2 weeks before disease onset. At that point, empirical treatment with doxycycline orally (4.4 mg/kg daily in 2 doses) was initiated based on the clinical suspicion of rickettsial infection.

The patient's serum and blood specimens taken on the 9th and 10th day of illness (before the initiation of doxycycline and one day after) were sent to the Aristotle University of Thessaloniki for rickettsiosis testing. Serum IgM antibodies against *R. typhi* were detected using an indirect immunofluorescence assay (Focus Diagnostics, Cypress, CA, USA) that revealed titers of 1:128 and 1:512 in samples taken on days 9 and 10, respectively. A low titer (1:64) of IgM antibodies against *R. rickettsii* was observed. DNA was extracted from the patient's blood specimen and PCR using rickettsia-specific primers amplifying a partial fragment of the 16S ribosomal RNA gene was applied (3). Sequencing of the PCR product and BLAST analysis (<https://blast.ncbi.nlm.nih.gov/>) showed that the causative agent was *R. typhi* (sequence 100% identical with those of other *R. typhi* strains, e.g. NR_074394 and CP003398).

Due to the fear of cosmetic staining of developing permanent teeth, treatment was changed to oral ciprofloxacin (30 mg/kg daily in 2 doses). Following 1 day of oral treatment with doxycycline and 1 day of oral treatment with ciprofloxacin, the patient's fever resolved and the maculopapular rash and other symptoms subsided. He continued the treatment with the same dosage of ciprofloxacin for 9 additional days. Re-examination of the patient 10 days later revealed a full clinical and laboratory recovery.

Murine typhus has been reported in Greece with most cases being recorded between May and October each year. The first study on murine typhus was reported in the country in 1992 and included 49 cases on Evia Island; 8 were pediatric cases (4). Two studies on murine typhus in Greece were focused exclusively on childhood cases (5,6). The first study reported on cases occurring during 1998–2000 in Heraklion City, Crete Island. Nine children 2–14 years of age were admitted with mild hepatosplenomegaly; the second study reported on cases occurring during 2001–2006 in Chania City, Crete Island, and included 41 children 1–15 years of age. Murine typhus in children has been reported also in Cyprus (7), and pediatric cases have been included in studies from Spain (8,9).

The diagnosis of murine typhus is challenging owing to the non-specific symptoms, which are usually mild. However, in a few cases, the disease may be severe and even fatal. In the present pediatric case, the initial mild symptoms were followed by rash and severe thrombocytopenia. Thrombocytopenia is present in a lower percentage of pediatric patients than adults (33% versus 69%, respectively) (10). Regardless of patient age, doxycycline is the treatment of choice for endemic typhus at a maximum dose of 100 mg twice daily and a total treat-

ment course of 7–14 days (11). Ciprofloxacin may be an alternative effective therapeutic agent (12). The current report shows the importance of a detailed medical history that in febrile cases with rash should always include questions about exposure to rats and fleas, although such a history may not always be present (6). Murine typhus is generally underdiagnosed in childhood (5). Although there are reports on infections caused by *R. conorii* (13,14), there has been no study on murine typhus in northern Greece. A seroprevalence study conducted in 2000 in various prefectures of northern Greece showed that IgG antibodies against *R. conorii* and *R. typhi* were detected in 1% and 2% of the population in Kavala Prefecture, respectively (15).

The classic triad of fever, headache, and rash is present in only one-third of the patients with murine typhs (1). In the present case, the absence of rash during the first week of illness together with the delayed information about the flea bites contributed to the delay in diagnosis. The rash and the unusual marked thrombocytopenia resolved soon after initiation of appropriate treatment. We report the present case to increase physicians' awareness of the disease even in areas not previously known to be endemic.

Conflict of interest None to declare.

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