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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, maculopapular rash was presented at the end of the first week of illness followed by marked thrombocytopenia. The detection of IgM antibodies against Rickettsia typhi and a positive PCR result in blood combined by sequencing confirmed the diagnosis of infection by Rickettsia typhi. Clinicians in northern Greece should be aware of the disease, even in cases presented with no specific initial symptoms.

Introduction
Murine typhus, also known as endemic typhus, is a flea-borne disease with a worldwide distribution, 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 (Leptopsylla segnis) serve as additional vectors. Humans are infected by inoculation of infective flea feces in bite wounds; 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). Due to non-specific symptoms, the clinical diagnosis and the laboratory confirmation of murine typhus is challenging, and may be delayed. This fact leads to underdiagnosis of the disease and unclear incidence.

Case report
In August 2016, a fully immunized 4-year-old boy, habitant of 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 advising the parents to re-examine the patient in case of fever persistence or deterioration of his medical condition. On day 3 the child was admitted again to the hospital with 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%), C-reactive protein 2.5 mg/dl (normal value <0.5), 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). Platelet count, renal function, and abdominal ultrasound examination were normal. Cefuroxime was prescribed (30mg/kg/24h in 2 doses) and the patient was sent home. On day 7, the patient returned to the hospital with high fever, chills, myalgia, severe headache and maculopapular rash. The patient had still abdominal pain and 2-3 episodes of vomiting and diarrhea daily, being unable to accept oral medical treatment. The rash began as maculopapular eruption on the trunk, with no petechial component, while on the next days it spread peripherally, sparing the palms and soles. On physical examination no lymphadenopathy was present, while neurological examination showed muscle weakness, although there was a difficulty in patient’s examination due to his mild psychomotor retardation. The patient was admitted to the Pediatric Clinic for further evaluation and treatment. Main laboratory findings were: 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) and aspartate aminotransferase 56 U/l, while alanine aminotransferase level, international normalized ratio and activated partial thromboplastin were at normal levels. No abnormalities were seen in chest X-ray and blood culture was negative for common pathogens. Empirical treatment was started with intravenous (IV) cefuroxime (90mg/kg daily in 3 doses). On day 9 (3rd day of hospitalization) the patient still had high fever, headache and widespread distinct maculopapular rash. New laboratory testing showed further decrease in platelets count (72,000/μl) and hemoglobin (11.3 g/dl), and increase of C-reactive protein (8.7 mg/dl). Due to the clinical and laboratory deterioration, the IV treatment was changed to ceftriaxone (100mg/kg daily in 1 dose), in fear of a bacterial infection resistant to cefuroxime. However, the characteristic triad of fever, headache and rash, accompanied with normal white blood cell count with 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 history of arthropod bites: initially they did not mention any bite, but finally they 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.

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 indirect immunofluorescence assay (Focus Diagnostics, Cypress, California) (titers: 1:128 and 1:512 in samples taken on day 9 and 10, respectively). A low titer (1:64) of IgM antibodies against *R. rickettsii* was observed. DNA was
extracted from patient’s blood specimen and a 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 (30mg/kg daily in 2 doses). Following 1 day of oral treatment with doxycycline and 1 day of oral treatment with ciprofloxacin, fever resolved and the maculopapular rash, as well as the 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 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 in childhood (5, 6). The first study reported on cases occurred during 1998-2000 in Heraklion city, Crete island. Nine children 2-14 years old were admitted with mild hepatosplenomegaly; the second study reported on cases occurred during 2001-2006 in Chania city, Crete island, and included 41 children 1-15 years old. Murine typhus in children has been reported also in Cyprus (7), while pediatric cases have been included in studies from Spain (8, 9).

The diagnosis of murine typhus is challenging due to 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 among 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 treatment course of 7 to 14 days (11). Ciprofloxacin may be an alternative effective therapeutic agent (12). The current report shows the importance of a detailed medical history which 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 is not any study on murine typhus from 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 only in one-third of the patients (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 about the disease even in areas not previously known to be endemic.
References


