

Human *Rickettsia aeschlimannii* infection: first case with acute hepatitis and review of the literature

A. TOSONI¹, A. MIRIJELLO², A. CIERVO³, F. MANCINI³, G. REZZA³, F. DAMIANO⁴, R. CAUDA⁴, A. GASBARRINI¹, G. ADDOLORATO¹, ON BEHALF OF THE INTERNAL MEDICINE SEPSIS STUDY GROUP*

¹Department of Medical Sciences, Internal Medicine and Gastroenterology Unit, Catholic University of the Sacred Heart, Gemelli Hospital, School of Medicine, Rome, Italy

²Department of Medical Sciences, IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Foggia, Italy

³Department of Infectious, Parasitic and Immune-mediated Diseases, Istituto Superiore di Sanità, Rome, Italy

⁴Institute of Clinical Infectious Disease, Catholic University of the Sacred Heart, Gemelli Hospital, School of Medicine, Rome, Italy

*Internal Medicine Sepsis Study Group: Michele Impagnatiello, Giovanna Passaro, Carla Vallone, Giulio Ventura, Vincenzo Zaccone

Abstract. – OBJECTIVE: *Rickettsia conorii* is responsible for the Mediterranean Spotted Fever. Recently, new rickettsial species have been recognized in Europe and implicated in human diseases. Clinical features often differ greatly from each other, but non-severe liver involvement is frequently observed during any rickettsial infection.

CASE REPORT: We describe the unique case of a patient presented with significant high aminotransferase levels due to the first human *R. aeschlimannii* infection ever detected in Italy. The hypothesis of rickettsiosis was made on the basis of a comprehensive medical history and was confirmed by serological tests. Molecular analyses made on a sample of hepatic tissue revealed the presence of a rickettsial species never found before in human liver.

CONCLUSIONS: A brief review of the literature is reported to highlight how relevant this case is and to remind that rickettsioses should be in the differential diagnoses of acute hepatitis, considering mostly the recent spread of new rickettsial species.

Key Words

Rickettsia aeschlimannii, Acute hepatitis, High transaminases, Rickettsiosis, Italy.

decade, other rickettsial species (i.e. *R. monacensis*, *R. massiliae*, *R. slovacica*, *R. helvetica*, *R. sibirica* and *R. aeschlimannii*) have been recognized in Europe and implicated as human pathogens¹. MSF is endemic in Southern Italy²; moreover, two cases of human rickettsioses due to *R. monacensis* and *R. massiliae* have been recently described^{3,4}.

Tick-borne spotted fever rickettsioses are characterized by headache, high-grade fever, cutaneous rash and the presence of the typical *tache noire*. However, in the early stages, symptoms are nonspecific: characteristic signs may be absent or unobserved, with an increased probability of misdiagnosis. Moreover, clinical signs may differ depending on the rickettsial species implicated.

Liver involvement is frequently observed during any rickettsial infection⁵. However, only a slight increase in aminotransferases is usually observed, with a rapid return to their normal blood levels.

Here, we report the first human case of rickettsiosis due to *R. aeschlimannii* in Italy, characterized by liver dysfunction and significant hyperaminotransferasemia.

Case Report

A 43-year-old man, with unremarkable medical history, developed low-grade fever, sore throat and asthenia while coming back home from a two-weeks summer holiday in Southern Italy. During this trip, he was in contact with wild animals (dogs).

Introduction

Mediterranean Spotted Fever (MSF) due to *Rickettsia conorii* represents the most common tick-borne rickettsiosis in Europe. In the last

A three-day antibiotic treatment with amoxicillin-clavulanate was prescribed without remission of symptoms. The patient soon developed a high-grade fever (peak 40°C) with left knee monoarthritis: an arthrocentesis was performed together with ceftriaxone treatment. A second arthrocentesis was performed 10 days later. Both specimens were sent for routine cultures and were reported negative. Because of high aminotransferase levels on laboratory evaluation, the patient was admitted to our Internal Medicine Inpatient Unit.

At admission, blood pressure was 140/80 mmHg, pulse rate was 85 beats/minute, oxygen saturation (SatO₂) was 97% in room air, temperature was 37.5°C. Mild, indolent, edema of the left knee was present; a very small ulcerated crust was found posteriorly on the left leg. No other symptoms (i.e. itch, headache or abdominal pain) were reported, nor other abnormal signs were present at the physical examination.

Laboratory findings showed markedly elevated aminotransferases (ALT 1388 u/L [normal value 7-45 u/L], AST 526 u/L [n.v. 7-45 u/L]), with mild cholestasis (alkaline phosphatase 217 u/L [n.v. 40-129 u/L], gamma-glutamyl transferase 183 u/L [n.v. 8-61 u/L], total bilirubin 0.6 mg/dL [n.v. 0.3-1.2 mg/dl]), prolongation of prothrombin time (INR 1.52 [n.v. 0.8-1.2]), mild thrombocytosis (platelet count 460 x 10⁹/L), and increase in acute-phase proteins (CRP 28 mg/L [n.v. <3 mg/L], ESR 108 mm [n.v. 0-9 mm]). Ten days after admission, aminotransferase levels reached their peak (ALT 2050 u/L, AST 798 u/L), with no significant increase in cholestasis.

No alcohol abuse history was detected. The patient was not on any regular medications and denied using over-the-counter drugs, weight loss or body building supplements, herbal medications or teas. A total amount of 5000 mg of oral paracetamol in 5 days has been needed to lower fever before admission, no more needed thereafter.

Serological assays for hepatitis A, B, C and E viruses were negative. Several diseases with a possible liver involvement such as bacterial infection with *Leptospira*, *Brucella*, *Salmonella*, *Borrelia*, *Treponema*, *Toxoplasma*, or viral infections with

CMV, EBV, HSV, HIV, *adenovirus*, *echovirus*, *coxsackievirus*, *Dengue virus*, or malaria and tuberculosis were excluded. Laboratory tests for autoimmune disease (anti-nuclear, anti-smooth muscle, anti-liver kidney microsomal, anti-neutrophil cytoplasmic and anti-mitochondrial antibodies) were negative, and so were blood, urine and throat cultures.

No abnormal findings were detected by abdominal ultrasound, and an echocardiogram was unremarkable.

The indirect fluorescent antibody (IFA) assay showed the presence of antibodies against *R. conorii*. However, only IgM (at a titer of 1/32) was present, while specific IgG antibodies were undetectable. Five days later, titers of IgM antibodies increased (1/64) and IgG antibodies became detectable (titer of 1/32). IgM and IgG antibodies were both at titers of 1/64 after 10 days.

The patient did not receive any antibiotic therapy, due to the well-known hepatic toxicity of anti-Rickettsia antibiotics; moreover, laboratory studies revealed a decrease in aminotransferase levels that was synchronous to the increase in antibodies titers (Table I).

A liver biopsy was performed: inflammatory and Kupffer cells hyperactivity was found, with no granulomatous lesions. A sample of hepatic tissue was sent to the *Istituto Superiore di Sanità, Department of Infectious, Parasitic and Immuno-mediated Diseases, Rome, Italy*, for molecular analyses. Rickettsial detection was determined by real-time PCR and classical PCR, using primers for *ompB* (outer membrane protein B) and *ompA* (outer membrane protein A) genes^{6,7}. *R. conorii* and *R. typhi* were used as positive controls. The pathogen identification was done by sequencing of PCR amplicons. The nucleotide sequences analyzed by the BLAST search tool (www.ncbi.nlm.nih.gov/blast), showed 100% identity with the *ompB* *R. aeschlimannii* strain MC16 (GenBank accession no. AF123705), and with the *ompA* *R. aeschlimannii* strain MC16 (GenBank accession no. U43800).

R. aeschlimannii was then identified as the cause of the illness in the patient reported here.

At 1-month follow-up, the patient recovered completely.

Table I. Time course of aminotransferase levels and antibodies titers.

Days after admission	0	5	10	15	30
ALT (u/L)	1388	1629	2050	1024	146
IgM	-	1/32	1/64	1/64	-
IgG	-	0	1/32	1/64	-

Discussion

R. aeschlimannii may have spread across Europe through infected ticks on migrating birds from Africa. These rickettsial organisms have been detected in ticks collected from several bird species in France, Germany and Italy^{1,8}.

The presence of this bacterium was also recently studied in central Italy during an entomological investigation conducted in the Insugherata Natural Reserve, localized in the urban area of Rome⁹. In that survey, *R. aeschlimannii* was found in questing ticks such as *Rhipicephalus turanicus* and *Ixodes ricinus*, demonstrating the maintenance of this pathogen in an area with favorable climatic conditions and susceptible hosts.

The first human rickettsial disease caused by *R. aeschlimannii* was documented in a French patient after a trip to Morocco¹⁰. Recently, the first autochthonous case of this infection in Europe was reported in a male patient from Greece with MSF-like symptoms¹¹.

To date, the case here reported is the second European case of *R. aeschlimannii* infection and the first rickettsiosis in Europe without MSF-like signs but with acute hepatitis, in which Rickettsia was detected by PCR performed on the hepatic tissue.

Liver involvement during rickettsial infection was not often matter of analysis, and a few manuscripts found in the literature are outdated. Studies do show a high frequency of liver dysfunction, which is usually mild or moderate, particularly during MSF¹². Few liver biopsies were performed, with the majority showing a granulomatous hepatitis histological pattern; no intact *Rickettsia conorii* was identified in the tissues by immunofluorescence¹³.

A more recent Italian study¹⁴ found elevated aminotransferase levels in about half of patients with MSF, that stabilized at the end of anti-rickettsial therapy and a Spanish study¹⁵ showed that anti-rickettsial antibodies are more commonly detected in patients with unexplained hyperaminotransferasemia than in healthy people.

Furthermore, the list of newly discovered *Rickettsia* species has grown rapidly in recent years and the clinical manifestations of these infections may be atypical and rarely severe, with liver involvement that should be recognized as soon as possible.

Understanding the pathogenic mechanism underlying the disease is made difficult by the small number of cases reported to date, although in this case it is reasonable to assume a direct injury to the liver caused by the microbe itself.

It would be interesting to determine whether the differences in the clinical features of rickettsial infections could be a consequence of genetic differences in the rickettsial strains as well as the result of differences in the genetics and environmental conditions of the host population or in rickettsial adaptation to diverse hosts and vectors.

In the case we presented, serological tests showed typical antibody trends following infection but with antibody titers lower than expected. This could be explained by the differences between antigen used in the IFA assay (*R. conorii* antigen) and *R. aeschlimannii* antigens; the lack of specificity between patient antibodies and IFA test antigen can determine low affinity in antigen-antibody interaction and consequently lower antibody titers detected by immunoassay.

Given these results, serological assays have been initially thought to be inconclusive, and liver biopsy became necessary in order to perform the histological assessment and molecular analyses of the tissue. In the meantime, we decided not to administer antibiotics but to “wait and see” the clinical course even considering the mild liver damage found on histology and the spontaneous recovery of the patient. The diagnosis of *R. aeschlimannii* infection was obtained retrospectively, when the patient had already shown a complete recovery and had been discharged.

This case supports the statement that liver biopsy is mandatory when medical history, laboratory tests and imaging are not sufficient to prove a diagnosis of acute hepatitis; moreover, liver biopsy currently has two more roles: for assessment of prognosis through staging disease, and to assist in making therapeutic management decisions¹⁶.

Conclusions

The infections caused by rickettsial species are emerging diseases, characterized by the possibility of liver involvement. Therefore, it is necessary to consider rickettsioses in the differential diagnoses of acute hepatitis.

Supportive foundations

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Conflicts of interest

The authors declare that they have no conflict of interests.

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