

Wien Med Wochenschr (2010) 160/3–4: 91–93
 DOI 10.1007/s10354-009-0733-1
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 Printed in Austria

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 Wiener Medizinische Wochenschrift

First described case of human granulocytic anaplasmosis in a patient in Eastern Austria

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Received April 30, 2009, accepted (after revision) November 18, 2009

Erster Anaplasmosen-Fall nach Zeckenbiss bei einem Patienten in Ost-Österreich

Key words: Anaplasma, fever, tick bite, thrombocytopenia, erythema

Zusammenfassung. Ein 64-jähriger Patient gelangt zur Aufnahme mit Fieber, Thrombozytopenie, erhöhten Leberenzymen und einem Exanthem am Stamm. Anamnestisch berichtet der Patient über einen Zeckenbiss vier Wochen vor Beginn der Symptome. Eine Erkrankung mit Meningokokken oder eine hämatologische Grunderkrankung wurden ausgeschlossen. Im Anschluss wurden serologische Untersuchungen hinsichtlich des Zeckenbisses durchgeführt. Die Ergebnisse zeigten einen hohen IgG-Antikörper-Titer für *Anaplasma phagocytophilum*. Nach einer Woche normalisierten sich alle Laborparameter und Symptome bildeten sich zurück. Der Patient erhielt keine Therapie und erholte sich komplett. Wir berichten über den ersten Fall einer Anaplasmosen in Ost-Österreich.

Schlüsselwörter: Anaplasmosen, Fieber, Zeckenbiss, Thrombozytopenie, Erythem

Summary. A 64-year-old otherwise healthy patient presented with high fever, thrombocytopenia, elevated liver enzymes and an erythema on the belly. The patient remembered a tick bite four weeks ago when walking with his dog before the specific symptoms started. A meningococcal disease or hematological illness was excluded. The serological results for tick-borne diseases showed a high IgG antibody titer for *Anaplasma phagocytophilum*. All symptoms and laboratory parameters normalized after one week of hospitalization. The patient received no treatment and recovered completely. This is the first confirmed case of human granulocytic anaplasmosis (HGA) in Eastern Austria.

Introduction

Tick-borne infections are emerging diseases in humans, comprising viral infections like tick-borne encephalitis (TBE) or borreliosis [1]. The increase in the incidence is not only due to the increasing leisure activities in the woods but also due to the global warming opening up new habitats for the ticks [2]. The most frequently present ticks in Europe are *Ixodes ricinus* and *Ixodes argas* [3]. Whereas TBE and borreliosis are well known in public, other less-known infections may be transmitted by ticks. Ticks may harbor other bacteria and protozoa, comprising *Rickettsia*, *Ehrlichia*, *Anaplasma* and *Babesia* [4]. In Europe, several forms of *Borrelia* species and *Rickettsia* are known which cause different diseases, all emerged through the past decades. In central Europe the most common tick-borne diseases like *Rickettsia* are caused by *Rickettsia slovaca* and *R. helvetica*. Human borreliosis in Central Europe is mostly reported to be caused by *Borrelia garinii* and *Borrelia afzelii* [5]. Human granulocytic anaplasmosis (HGA) is a rare disease and only a few cases have been reported in Europe, the first case in Slovenia in 1997 [6]. However, the number of cases for tick-borne disease apart from borreliosis in central Europe is still fewer. Wild life animals, mice or deer, are the natural host of these microorganisms. There have been several reservoirs described, mostly wood

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mice, and also mammals such as dogs, sheep, lambs, goats and horses. The prevalence of *Anaplasma phagocytophilia* in ticks is dependent on the geographic region and ranges between 0.5 and 66%. In Austria, the prevalence is relatively high and is described with around 14% [7]. Recently a study of *Anaplasma phagocytophilia* in German dogs revealed a prevalence of 42.3% [8]. Although ehrlichiosis was mainly reported in animals, there are a few areas where *Anaplasma* is endemic [9]. In 2008 a series of serological studies of human anaplasmosis infection in Slovakia was published and underlined that *Anaplasma* should be considered a differential diagnosis in tick bites especially in cases of acute febrile illness [10].

Human granulocytic anaplasmosis (HGA) (previously known as human granulocytic ehrlichiosis) caused by *Anaplasma phagocytophilum* and human monocytic ehrlichiosis caused by *Ehrlichia chaffeensis* or *E. ewingii* are rare tick-borne infections, generally afflicting immunocompromised patients [11]. Formerly classified taxonomically into the group of rickettsia, both genera are distinct. *Anaplasma* and *Ehrlichia* are obligate intracellular gram-negative bacteria. Whereas *Ehrlichia* affects monocytes, *Anaplasma* infects granulocytes. Very often they form intracytoplasmic clusters of bacteria (morulae), which are seen in between 20 and 80% of patients with acute illness.

The first confirmed case of *Anaplasma* in Europe was described in 1997 in Slovenia [6]. After that, many European countries reported cases of *Anaplasma phagocytophilia* in humans. The United States also reported cases of ehrlichiosis. Nevertheless, the clinical course seems to be slightly different. The vector of ehrlichiosis in Europe is *Ixodes ricinus*, which also causes Lyme borreliosis. Usually it is not a human disease, but the infection of human is mostly accidental.

In Western Austria, a few cases of *Anaplasma* infections have been confirmed, but no case in the region around Vienna has been found. This is the first report of human anaplasmosis in Eastern Austria.

Case report

A 64-year-old male patient was admitted to the clinical ward of the Division of Infectious Disease, because of high fever, thrombocytopenia and morbilliform erythema on the belly. His past medical history included hypertension and hypothyreosis.

He was a dog owner who took his dog for a walk twice daily. About 4 weeks ago he recognized a tick bite

on his belly, after a walk with his dog in the woods south of Vienna. Two weeks later an erythema migrans-like rash showed up around the former tick bite. Furthermore, he had fever around 39 °C. His physician prescribed him amoxicillin 1 g twice a day for eight days. During this medication he recognized an improvement of the rash but still had higher temperatures around 38°. On day eight of treatment with Amoxicillin the rash worsened, spreading all over his limbs and up to the neck. He was then presented to the emergency department and admitted to the ward with the differential diagnosis meningococcal disease, some hematological illness, or amoxicillin-induced exanthema. Amoxicillin was stopped. The patient received no further antimicrobial treatment.

He presented with elevated creatinine (1.39 mg/dl), slightly elevated liver enzymes and bilirubin (GOT 37 U/l, GPT 49 U/l, bilirubin 1.09 mg/dl), elevated LDH (256 U/l), thrombocytopenia (89 G/l) and elevated C-reactive protein (CRP 6.54 mg/dl). The leucocyte count was 7.05 G/l. The differential count showed a mild neutrophilia of 80%. Meningococcal disease was excluded by the previous antimicrobial treatment and subsequently negative blood-cultures. Serum antibodies were determined for *Anaplasma phagocytophilum*, *Borrelia burgdorferi*, *Rickettsia conorii*, CMV, Parvo Virus and EBV on the day of administration. DNA tests for *Ehrlichia phagocytophilum* and *Borrelia* sp. were also run.

Three days after admission the high fever stopped and the rash vanished. Thrombocytes were still low until day three (79 G/l) and returned to normal on day five. Liver function tests, serum creatinine and CRP normalized spontaneously after one week. Patient was sent home after five days.

The serological results showed an IgG antibody titer of 1:1024 for *Anaplasma phagocytophilum* in the IFA test. This is 16-fold higher than the cutoff point. PCR for *Anaplasma* in the blood sample was negative.

Borrelia IgM antibodies (IB) and IgG antibodies (rEIA, IB) were also positive. The clinical and laboratory results of this patient fulfilled the criteria of confirmed anaplasmosis. This suggests an acute stage of illness. The patient was observed in the outpatient setting and received no treatment, as the clinical symptoms resolved.

Discussion

Anaplasma phagocytophilia occurs internationally. In Europe the first confirmed case of *Anaplasma* was

described in 1997 in Slovenia [6], followed by cases in Sweden [12], Spain [13], the Netherlands [14] and Poland [15]. In Western Austria five cases were described in the area of Innsbruck [16]. The HGA agent is transmitted by *Ixodes ricinus*, which is the most common tick-species in Austria. In most cases patients with HGE have a history of a tick bite between 7 and 30 days before the onset of disease [17]. The usual clinical presentation consists of flu-like syndromes (fever, headache, and arthralgia), gastrointestinal manifestations (nausea and diarrhea), hepatosplenomegalia, hematological abnormalities and sometimes a rash. A rash occurs more often in patients with monocytic ehrlichiosis, in HGA only a few cases were described in Europe [12].

In our patient it was surprising that he presented with a rash as the major clinical symptom. Self-limiting thrombocytopenia, a slight leucocytopenia and elevated serum transaminase activities are typical for infections with *Anaplasma*. The history of a tick bite together with the general appearance is suggestive for *Anaplasma*. As a differential diagnosis *Babesia* and *Ehrlichia* could be considered. Infections with *Babesia divergens* and *Babesia microti* usually have other symptoms and present with hematuria and hemolysis [18].

Diagnosis of human anaplasmosis requires careful consideration of symptoms and laboratory parameters. HGE may be confirmed as by Center of Disease Control case definition by either serological evidence of a fourfold change in IgG-antibody titer or PCR or detection of anaplasma antigen in a biopsy sample, or peripheral blood smears [19]. Serology by IFA is the most common diagnostic technique. Serology may give false positive results and has cross-reactions with other rickettsial diseases [20]. Detection of *Anaplasma* by PCR is a rapid and sensitive test. However, literature showed that a negative PCR does not exclude the diagnosis [17]. The test for detection of morulae, intracellular clumps of infected circulating leucocytes, has a high specificity but low sensitivity [21]. Morulae are usually found only in the acute febrile episodes and are in accordance with the experience of the microscopist.

In our patient serology for IgG antibody was sixteenfold higher than the cutoff, which confirms together with the clinical appearance the diagnosis of HGA. The PCR for *Anaplasma* was negative. This is not a surprising constellation because in literature 27% of European cases showed a positive serology and PCR negativity. In healthy not immunocompromised patients anaplasmosis is a self-limiting disease usually without clinical symptoms.

This is the first confirmed case of human granulocytic anaplasmosis in a patient in Eastern Austria.

Anaplasma phagocytophilia should be considered as differential diagnosis in patients with tick bites.

Conflict of interest

There is no conflict of interest of all authors regarding the submitted manuscript.

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