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Human granulocytic anaplasmosis (HGA) – diagnostic and therapeutic recommendations. Analysis of a clinical case

Rekomendacje postępowania diagnostycznego i terapeutycznego w ludzkiej anaplazmozie granulocytarnej (HGA) – analiza przypadku

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Key words

tick-borne diseases, human granulocytic anaplasmosis (HGA), doxycycline

Słowa kluczowe

choroby przenoszone przez kleszcze, ludzka anaplazmoza granulocytarnej (HGA), doksycyklina

S u m m a r y

Human granulocytic anaplasmosis (HGA), tick-borne diseases, gives a variety of clinical symptoms what makes diagnosis difficult. Moreover, according to recent reports in the literature affecting more and more patients. Increasing incidence is associated with higher recreational activity wooded areas. Incorrect diagnosis and hence incorrect treatment of the infection, may lead to death of the patient. Taking into account the differential diagnosis of tick-borne diseases should be aware of HGA.

We present a case report of patient who had been bitten by a tick and after a few days presented fever, stomachache, arthralgia and muscle aches. Many other diseases entities responsible for these symptoms were taken into account in the differential diagnosis.

Therapeutic decision was based upon history, physical examination and results of additional laboratory tests. Immediate clinical improvement occurred after administration of doxycycline. Based on current guidelines of European Society of Clinical Microbiology and Infectious Diseases (ESCMID) certain diagnosis was established few months later after hospitalization, by serological test due to demonstrate the presence of IgM antibodies and a decrease IgG antibodies to *Anaplasma phagocytophilum*. Article contains current diagnostics and therapeutic recommendations for anaplasmosis.

S t r e s z c z e n i e

Przenoszona przez kleszcze ludzka anaplazmoza granulocytarnej (HGA) charakteryzuje się bardzo szerokim spektrum objawów klinicznych, co sprawia, że jest chorobą, której rozpoznanie może być bardzo trudne. Ponadto, jak wskazują najnowsze doniesienia w literaturze, dotyka coraz większej grupy pacjentów. Rosnąca częstotliwość zachorowań wiąże się ze wzrostem aktywności rekreacyjnej populacji na terenach zalesionych.

Niewłaściwe rozpoznanie, a co za tym idzie, nieprawidłowe leczenie zakażenia może prowadzić do zgonu pacjenta. Biorąc pod uwagę diagnostykę różnicową chorób odkleszczowych należy pamiętać o HGA.

Opisywany w artykule przypadek dotyczy pacjenta, u którego w kilka dni po ukąszeniu przez kleszcza wystąpiły: gorączka, bóle mięśni i stawów oraz objawy ze strony przewodu pokarmowego (ból w nadbrzuszu). Diagnostyka różnicowa obejmowała szeroki wachlarz jednostek chorobowych, w których występują te nieswoiste objawy kliniczne. Decyzje terapeutyczne podjęto w oparciu o wywiad, badanie fizykalne oraz wyniki badań dodatkowych. Po zastosowaniu w terapii doksycykliny uzyskano szybką poprawę stanu klinicznego. Wykazanie obecności przeciwciał anty-*A. phagocytophilum* w klasie IgM oraz spadek przeciwciał w klasie IgG po kilku miesiącach od hospitalizacji pozwoliło, zgodnie z rekomendacjami European Society of Clinical Microbiology and Infectious Diseases (ESCMID), na pewne rozpoznanie ludzkiej anaplazmozy granulocytarnej. W artykule omówiono aktualne rekomendacje diagnostyczno-terapeutyczne dotyczące anaplazmozy.

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INTRODUCTION

Human granulocytic anaplasmosis (HGA) is an acute, bacterial disease caused by *Anaplasma phago-*

cytophilum. Pathogen is an obligatory intracellular, Gram-negative bacterium. The main location of existence *A. phagocytophilum* are neutrophils, endothelial

cells and macrophages. Formerly it was classified as *Ehrlichia phagocytophilum* and was recognized as an animal pathogen. The first case of HGA was described in the USA, Minnesota in 1990 (1-4).

A. phagocytophilum is classified in the *Anaplasmataceae* family, in the order Rickettsiales, the class *Alphaproteobacteria*. The species was isolated in 2001 through molecular research (importance of genes 16SrRNA, groESL) (5, 6).

In Europe reservoir for microorganism are deers, roe-deers, and less often cattle, horses and goats. There are two possible routs of transmission, more common by tick-bite, the second way – by contact with internal organs of infected animals, that is typical for butchers, hunters and foresters (4, 5, 7).

A. phagocytophilum in Europe is transmitted by saliva and excretions of ticks e.g.: *Ixodes ricinus*, *Dermacentor reticulatus*, *Ixodes persulcatus* and *Ixodes trianguliceps*. Pathogens spread through blood and lymph vessels, infect neutrophils, endothelial cells and macrophages. *A. phagocytophilum* possess an affinity for sialylated and fucosylated proteins found on the surface of granulocytes. The P44/Msp2 proteins are major surface antigens and they are useful for serodiagnosis (6, 8). Bacterium is capable of blocking function within the lysosomal vacuoles where may amplify and form the morulae (characteristic mulberry – like bacterial clumps). Then, pathogen re-enters the bloodstream, reduces the production of peroxides, inhibits apoptosis of neutrophils (8, 9). Moreover, degranulation of neutrophils enhance inflammation (10).

High activity of proinflammatory cytokines IL-1B, IL-6, TNF α , INF α accompanying the increase in the number of lymphocytes TH1 is important in the inflammatory reaction (8, 9, 11). Furthermore, the infection causes a decrease in the number of CD4, CD8, abnormal migration and phagocytosis. Such action pathogen can cause suppression of the immune response of the host, and thus, increases the risk of opportunistic infections (12).

The clinical course of *A. phagocytophilum* infection is variable and depends on many factors, including the presence of concomitant diseases, infections and additional tick-borne pathogens.

CASE REPORT

77 years old, Caucasian male patient, working as a farmer on areas endemic for tick-borne diseases (e.g. Lyme disease) was admitted to Infectious Diseases Department with one week history of fever, chills, strong abdominal pains, head and muscle ache. Since 6 days he had been taking Amoxicyclin 1 g twice a day. Three weeks ago he was bitten by a tick. No one from close contact had similar symptoms. Prostatectomy in aged 62 and appendectomy in aged 56 was reported in his previous medical history. He suffers from hypertension. On the first day after admission patient complained of strong stomachache, with no relation between meals, localized in right upper quadrant of abdomen, chills, headache, and muscle ache of lower limbs.

Leukopenia 3.51 K/ul, limfopenia 0.92 K/ul, thrombocytopenia 68 thous./ml were found in laboratory tests. Urinalysis showed numerous bacteria and strands of mucus. Blood levels of important parameters were as follow: glucose 156 mg/dl, urea 55.9 mg/dl, CRP 84.25 mg/l, D-dimer 3746.97 ug/FEU (normal range up to 500 ug/FEU), activity of ALT 42 U/l, AST 32 U/l. In the abdominal ultrasound examination enlarged liver without focal lesions, small precipitation in the gall bladder, bilateral cysts around renal calyx in kidneys were described.

Chest radiograph revealed fibrosis in left costophrenic angle, besides, without any other abnormalities. Blood culture was sterile. Paul-Bunnell-Davidsohn test was negative, just as immunoglobulin class IgM against CMV. Second day tests indicated the progression of thrombocytopenia to level 53 thous./ml.

In the urine analysis protein 75 mg/dl, urobilinogen 1 mg/dl, bilirubin 1 mg/dl were identified.

In control morphology of the blood, on the third day of hospitalization, anemia HGB 10.5 g/dl and leucopenia 3.86 K/ul were presented. In manual blood smear segments dominated (85%), percentage distribution of the other cells presented as follows: limfocytes – 8%, monocytes – 7%, eozynofiles – 4%, bazofiles – 1%.

Serology tests for *Babesia microti* and *Anaplasma phagocytophilum* were ordered.

Empiric therapy with doxycycline in dose 200 mg twice per day and was included in addition to symptomatic treatment. After 5 days of hospitalization patient was discharged from the hospital and ambulatory continuation of the antibiotic therapy was ordered. His condition improved. Infection of *Anaplasma phagocytophilum* was suspected by epidemiologic history and positive result of serologic test for specific IgM 160 U/ml (positive from 20 U/ml), IgG 2048 U/ml (positive from 64 U/ml) which we received on the third day.

Renewed detection of immunoglobulin class IgG after 5 months gave result 64 U/ml, what indicate on 32-fold drop and according to recommendations of European Society of Clinical Microbiology and Infectious Diseases (ESCMID) confirms diagnosis. Further serology tests were negative.

DISCUSSION

HGA is a tick-borne disease with the world-wide prevalence, including United States, Europe and Asia (2). Clinical manifestations are not-specific. The meta-analysis from 10 studies describing cases of HGA across Europe and North America presented by Dumler et al. which comprise 685 patients, shows that major symptoms are fever (92% in America, 98% in Europe), headache (73% in America, 89% in Europe), myalgia (79% in America, 65% in Europe), malaise (96% in America, 47% in Europe) and thrombocytopenia (72% in America, 64% in Europe) with elevated activity of ALT or AST (79% in America, 51% in Europe) as most common form laboratory abnormalities. The less common

are symptoms from gastrointestinal track, cough, arthralgias, stiff neck, confusion and skin rash (1).

Epidemiological history is of key importance for the diagnosis. One must remember, the patients often do not remember the tick-bite.

The predominant symptoms of the disease in our patient were fever chills, abdominal pain, myalgia limbs, headaches. In physical examination ascertained hepatomegaly. Laboratory abnormalities were leucopenia and thrombocytopenia. Differential diagnosis included pneumonia, sepsis, *Babesiosis*. On the basis of additional tests excluded the above-mentioned diagnostic hypotheses and 32-fold antibody levels decline after five months from the first symptoms of the disease, the case meets the criteria for a confirmation of HGA.

Diagnostic criteria to confirm case of anaplasmosis, according to European Society of Clinical Microbiology and Infectious Diseases (ESCMID 2004) are:

seroconversion \geq 4-fold change antibodies titer

or:

positive PCR assay demonstrating *A. phagocytophilum* specific DNA in blood

or:

isolation of *A. phagocytophilum* in blood culture.

Criteria of probable case of anaplasmosis according to European Society of Clinical Microbiology and Infectious Diseases (ESCMID 2004):

febrile illness with a history of tick bite or tick exposure and:

presence of significant *A. phagocytophilum* antibodies titer

or:

presence of intracytoplasmic morulae in a blood smear.

The current recommended therapeutic regimens for HGA is administration of doxycycline or tetracycline for 5-14 days. Doxycycline in dose 2 x 100 mg per day is the first choice treatment anaplasmosis and should be applied 5-14 days. Tetracycline should be administered orally at 6-h intervals at a dosage 500 mg. Doxycycline is better tolerated than tetracycline.

Not recommended for use betalactams, co-trimoxazole, macrolides. When there is suspicion of co-infection with *B. burgdorferi* is recommended to use doxycycline for 14 days.

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