THE INFECTION CAUSED BY RICKETTSIA CONORII (CASE PRESENTATION)

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Abstract: Boutonneuse Fever is usually a benign rickettsial disease caused by **Rickettsia conorii** *(endemic in the Mediterranean basin); however, severe complications can occur in elderly and in immunologically-compromised persons (the so-called malignant butonneuse fever). Mild forms are usually observed in children. The major clinical features are fever, exanthemas, and "tache noire" (black scar/mark, necrotic plaque), myoarthralgias and renal failure. The positive diagnosis is confirmed by using culture techniques or serologic tests; the antibody detection by immune-fluorescence is possible only later in the infection evolution. The election treatment consists of cyclins, luoroquinolones, chloramphenicol and the new macrolides. We present a case of Boutonneuse Fever originating from a non-endemic area and the diagnosis problems. (In Romania the BF is endemic in Constanta and Bucharest).*

Keywords: Boutonneuse Fever, **Rickettsia conorii, clinical trial**

Rezumat: Febra butonoasă (FB) este o rickettsioză benignă, produsă de Rickettssia conorii (endemică în bazinul mediteranean), cu posibile complicaţii apărute la persoane imunocompromise sau vârstnici (aşa-numita formă malignă de febră butonoasă). La copii evoluează uzual ca forme medii de boală. Tabloul clinic se caracterizează obişnuit prin febră, exantem şi pata neagră (escara sau placa necrotică), mioartralgii, insuficienţă renală. Diagnosticul pozitiv se confirmă prin cultură sau teste serologice, detecţia anticorpilor prin imunofluorescenţa fiind posibilă tardiv în evoluţia infecţiei. Tratamentul de elecţie constă în administrarea ciclinelor, fluorochinolonelor, cloramfenicolului, macrolidelor noi. Prezentăm un caz de febră butonoasă, provenind din arie nonendemică şi problemele de diagnostic (în România FB este endemică în Constanţa şi Bucureşti).

Cuvinte cheie: febra butunoasă, Rickettssia conorii, caz clinic

INTRODUCTION

Boutonneuse Fever is caused by Rickettsia conorii and is transmitted through the bite of the dog tick - *Rhipicephalus sauguineus*, being characterized by fever, myalgias, headache, generalized maculopapulous exanthema and inoculation scar (the black spot) at the bite place.

The evolution is generally benign, but in approximately 6% of the cases, the BF advances accompanied by a multiple organic insufficiency, neurological manifestations (confusion, ataxia, dysarthria) and mortality in 2,5-5% of cases. The disease has a seasonal character, occurring in spring and summer in the Mediterranean area and around the Black Sea. In our country it has been diagnosed in Dobrogea.

The Mediterranean Spotted Fever, characterized by the infection of the vascular endothelium is in fact the attribute of a micro vascular and vasculitic injury.

Ethyopathogeny. R. conorii is an α-proteobacteria with a compulsory intracellular tropism, able to adhere and invade a variety of cells, both in vitro and in vivo; in the latter case, the human endothelial cells react by altering the presentation of the adhesion molecules, releasing cytokines and the HO hemoxygenase, which will influence the synthesis of prostaglandins via the COX cyclooxygenases, thus contributing to the vasodilatation and the permeability alterations occurring during the disease.

The endothelial cells are building a semi permeable barrier at the very limit between the blood vessels and the interstitial compartment, having a major role in maintaining homeostatasis; in the pathogenesis of the BF, the oxidative stress and the defensive anti-oxidant enzymatic system are considered decisive, as they control the system of the cyclooxygenase, which is responsible for the release of the vaso-active substances: prostaglandins, prostacyclins and thromboxanes, respectively.

The connection of the R. conorii to the cellular membrane is achieved through the participation of several proteins, certainly involving the surface protein OmpB and Ku 70, which will recruit the ubiquitin ligase in the host cell, resulting in the intracellular rearrangement of the actin, its polymerization, respectively, via the RickA protein group. The cellular destruction has multiple factors and it is accompanied by a release of reactive oxygen species (ROS) and the reduction of the enzymes involved in the protection of oxidative injury. Following the ROS-mediate cellular lesions, an increase of the micro vascular permeability occurs due to the direct action of

rickettsia, but also due to the action of the pro-inflammatory cytokines and possibly due to the coagulation factors being activated by the alterations of the endothelial junctions. It is considered that, besides the alterations occurring in the status of coagulation in the acute phase, the patients also face an alteration of the cell-mediated immunity, with the reduction of the CD4 lymphocytes and the alteration of the cytokines profile. Fractalkine (CX3CL1) is a chemokine, expression of the endothelial cells, the major target of the R. conorii. The peak of the CX3CL1 expression on the third day of infection coincides with the macrophage infiltration of the infected tissues and precedes the peak of the rickettsia at tissue level.

The clinical manifestations are difficult to interpret in the absence of the epidemiologic context, taking into consideration that only 37% of the patients have recently experienced a tick bite, but 89% have got in touch with dogs or travelled to endemic areas.

In the first week, the patients show pseudo-influenza symptoms, with 39-40° C fever, myalgias, headaches along with a generalized non-itching tegument eruption, to be found mostly at limbs level, 2-6 days after the fever outbreak, arthralgia or myoarthralgias. In about 45 % of the cases, the clinical picture is completed by the thrombocytopenic purple, while the primary affect (the scar or the black spot), i.e. the spot of the tick bite is obvious in 71 % of the cases.

From the biological point of view, one can find thrombocytopenia, hepatic cytolysis, renal characteristics alteration (the creatinine level is higher than 150 mmol/L, hyponatremia, hypocalcaemia and hypoxemia.

The confirmation of the Boutonneuse Fever is made through immune-fluorescence, i.e. the identification of the IgM and IgG antibodies in dynamics, both in the acute phase and in convalescence, with a four-time growing of the antibody titre.

The election treatment consists of cyclins, fluorochinolones or chloramphenicol for 7-14 days, according to the severity of the clinical manifestations.

Possible complications may occur with immune-compromised or elderly patients in cases of renal insufficiency by acute tubular necrosis, interstitial glomerulonephritis, respiratory insufficiency, gastrointestinal haemorrhages, infectious shock, vein thrombosis, athromyalgias, arthritis, exceptionally pulmonary complications, meningoencephalitis, myelytis and paraplegia. The prognostic is generally good, except for the immune-compromised or elderly patients, in which the mortality rate is about 5%. There is no vaccine for the BF, but the prophylaxis is possible through a dose of azythromycin. One should also focus on the education of the people living in the endemic areas, concerning their close contact with dogs or possibly parasitized sheep.

Case presentation

Patient B.D., 48 years old, residing in Băile Olănești, Vâlcea, is transferred from Râmnicu-Vlâcea Hospital, in order to elucidate a one-week long feverish syndrome, accompanied by chills, skin eruption about to generalize, myoarthralgias, headache – symptoms required his hospitalization between 13-16 June 2008 to the infectious diseases department. The patient's condition evolution is unfavourable, his general state worsened progressively, which suggested a severe sepsis, while he was under betalactams and aminoglycosides treatment.

In the patient's personal history, we found a spastic paraparesis, a cervical spondilosis and a chronic tobacco-related bronchitis. The patient admitted having smoked and the alcohol consumption, but he did not leave his hometown, he did work physically, he has got a dog but he has no sign of recent tick bite.

The objective examination upon his hospitalization in our clinic (June 17, 2008) revealed the following: fever 39°C, medium-worsened general condition, erythematic face, presence of a maculopapular skin eruption lightly nodular during palpation, erythematic, which did not disappear upon finger pressing. The eruption is not itchy, but generalized, more visible on thorax bottom, abdomen and superior and inferior limbs; constitutionally hyper-pigmented skin, diffuse myoarthralgias; pulmonary stetho-acoustics: bilateral bronchitic rhonchi, tachycardic heart noises, AV=92/min, TA=110/60mmHg, sensitive abdomen during palpation in the right hypocondrium, liver with its inferior edge 3 cm under the right rib board and the superior edge in the right intercostal V space, elastic consistence, polakyuria, nycturia, slight motor deficiency in both inferior limbs, no signs of meningeal irritation.

Picture no. 1. Maculopapular skin eruption

The para-clinical examinations revealed the following: WBC=9.990/mmc, Ne=44.1%, Ly=29.1%, Mo=24.1%, Ba=2.6%, Eo=0.1%), E=4.46mil/mm^3, Ht=38.8%, Hb=13.2g/dl, MCV=87.0fl, MCH=29.6pg, MCHC=34.0g/dl, Tr=207.000/mmc, ASAT=111U/l, ALAT=150U/l, FA=78U/l, amylase=79U/l, GGT=163U/l, BD=0.1mg/dl, BT=0.29mg/dl, ASLO=64.6U/l, ESR=29mm/h, fibrinogen=282mg/dl, PCR=88.6mg/dl, all the bacteriological examinations (haemoculture, uroculture, sputum culture, nasal-pharyngeal exudates) being sterile.

The serological examination, i.e. the identification of the IgM antibodies for Rickettsia conorii was intensely positive, with a growth in dynamics of the antibody titre.

Clinical data: infectious syndrome, algesic syndrome, the characteristic skin eruptive syndrome,

papular-erythematic and having a generalized non-itching "boutonneuse" aspect, hepatomegaly; biological data: the bacterial-type inflammatory syndrome, moderately present and the hepatocytolisis syndrome, partly determined by the alcoholic hepatitis made us suggest (even in the absence of a conclusive epidemiological investigation - the provenance from a well-known endemic area for BF, the lack of tick bite) the diagnosis of Boutonneuse Fever, which was confirmed serologically by the presence of a high titre of acute-phase antibodies for Rickettsia conorii.

The evolution of the case was promptly favourable under treatment, hygienic-dietary conditions and short- time cortisone therapy; Cyprofloxacinum 1g/day for 7 days and after that in ambulatory care, influenced by the patient's background, immune-depressed; symptomatic treatment, reaching a feverless stage and the disappearance of the eruption in the first days of treatment.

The diagnostic particularity and difficulty lies in the emergence of the BF in a region of the country where such a disease was not considered possible, in a patient without a positive epidemiological investigation (tick bite, primary scar, satellite adenopathy), with severe clinical manifestations, in which the initiation of the aetiological therapy led to a favourable evolution, although the initiation was performed one week after the debut.

The case presented above brings back to our attention those rare infectious diseases, whose natural endemic distribution is continually changing, making us re-evaluate the endemic areas for different pathogen agents, vector-borne or not.

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