Prolonged course of hepatic granulomatous disease due to Bartonella henselae infection

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Abstract

Cat-scratch disease (CSD) is an emerging zoonosis caused by Bartonella henselae. The disease is usually self-limiting and typically presents in about 90% of all cases as a subacute regional lymphadenopathy. We present a case report of an unusual CSD presentation, persistent hepatic granulomatous disease due to Bartonella henselae infection despite combination therapy with doxycycline and rifampicin. Furthermore, a review of literature was conducted. (Acta gastroenterol. belg., **2016**, 79, **497-499**).

Key words : bartonella henselae, cat-scratch disease, lymphadenopathy, PCR, differential diagnosis, hepatosplenic disease.

Introduction

CSD (cat-scratch disease) occurs worldwide and is the most common cause of infectious lymphadenitis in children, adolescents, and young adults. The disease is usually self-limiting and typically presents in about 90% of all cases as a subacute regional lymphadenopathy. However, in 10%, a broad spectrum of atypical systemic symptoms can develop (1-3). We report a case of an unusual CSD presentation, confirmed by specific serology and molecular analysis. In addition, a review of literature was conducted to inform healthcare professionals on the various clinical presentations of *Bartonella henselae* infections, the diagnostic techniques, and the therapeutic challenges.

Case report

In March 2015, a 35-year-old Caucasian male was admitted with respiratory bound upper-right abdominal quadrant and referred right shoulder pain since three weeks. He mentioned a non-intentional weight loss (17 kilograms over the last four months) and night sweats without fever. He presented with normal vital signs. There was no history of recurrent cough nor loss of appetite. He works as a metal welder, smokes cigarettes (10 pack-years) and uses cannabis (daily basis). No recent trauma or any foreign travel was reported. He used to bread rabbits and has a domestic cat which was recently treated for fleas. His medical history included an episode of non-differentiated bilateral elbow arthritis, an acromioplasty of the right shoulder, and a recent influenza A infection followed by diffuse arthralgia. On physical examination tenderness of the upper-right abdominal quadrant, normal right shoulder mobilization and a few small palpable axillar lymphadenopathies were noticed. Laboratory results revealed a leukocytosis (11 x $10^3/\mu$L with 76% neutrophils ; normal 1.0 – 4.8 x $10^3/\mu$L), elevated erythrocyte sedimentation rate : 54 mm/h ; normal < 15 mm/h) and a mild elevation of alkaline phosphatase (ALP) : 191 U/L ; normal < 129 U/L and gamma glutamyltransferase : 63 U/L ; normal < 61 U/L with normal aspartate aminotransferase : 13 U/L ; normal < 40 U/L and alanine aminotransferase : 17 U/L ; normal < 41 U/L value. Urinalysis, auto-immune serology, molecular sexual transmitted disease testing, and respiratory pathogen screening were normal. Contrast-enhanced abdominal CT-scan exposed diffuse hepatosplenic lesions with adjacent edema and multiple reactive intra-abdominal lymphadenopathies (Fig. 1). Thoracic CT-scan showed multiple enlarged lymph nodes in the axillae, the cervical basis and mediastinum without typical lung pathology, suspected for systemic granulomatous infection. An ultrasound guided biopsy of a subcapsular liver lesion revealed necrotizing granuloma formation (Fig. 2). Microbiology testing showed Gram-negative coccobacilli on Gram staining, without growth on routinely used bacteriological media with limited (3/5 days of) incubation time. Acid fast (auramine) and fungal staining were negative. PCR *M. tuberculosis* complex on the liver tissue was negative. In the histopathological lab, Grocott, PAS (periodic-acid-shift), Ziehl-Neelsen, and Steiner staining couldn't reveal any micro-organism. The liver granulomata with central necrosis were CD68+. Blood cultures remained negative. Further differential diagnostic testing for plausible causative agents of hepatic granuloma formation was conducted (Table 1). Serologic testing for *Treponema pallidum, Brucella species, Coxiella burnetti,*

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Table 1. — **Plausible causative agents of hepatic granuloma**

Infectious	
Bacterial	M.tuberculosis, M.bovis, Brucella spp, Treponema pallidum, F.tularensis, L.monocytogenes, Bartonella henselae, C.burnetii, M.leprae, C.psittaci, T.whipplei, B.pseudomallei, Y.enterocolitica
Viral	Cytomegalovirus, Epstein-Barr Virus, HIV, Hepatitis B and C
Parasitic	T.gondii, S.mansoni, S.intercalatum, Toxocara canis/cati, Ascaris suum, Leishmania spp, F.hepatica, Plasmodium spp, E.histolytica
Fungal	H.capsulatum, C.immitis, C.neoformans, N.asteroides complex, Candida spp, Aspergillus spp, B.dermatitidis
Non infectious	
Sarcoidosis	
Primary biliary cirrhosis	
Malignancy	Hodgkin's disease, lymphomas
Metal intoxication	
Vasculitis	Disseminated Lupus erythematosus
	Rheumatoid arthritis
	Polyarteritis nodosa
	Rheumatoid arthritis
	Wegener's disease
Drug reaction	
Corpora aliena reaction	

Toxoplasma gondii, Strongyloides, Echinococcus, Schistosoma, Cryptosporidium, Giardia, Entamoeba histolytica, Filaria, Schistosoma, Cytomegalovirus, hepatitis B, hepatitis C and Human Immunodeficiency Virus remained negative such as interferon gamma release assay and small intestine biopsy for Whipple's disease. Serologic markers of past Epstein-Barr virus were positive. Chronic granulomatous disease was excluded by neutrophilic function analysis and bone marrow analysis was strictly normal. Histopathological examination of the bone (trabecular bone, diameter 1 cm) was normal. A highly elevated *Bartonella henselae* serology was found with cross reactivity for *B. quintana* immunoglobulins. Indirect fluorescent assay (IFA) testing revealed *B. henselae* Immunoglobulin (Ig) G : 1/16000, *B. quintana* IgG : 1/8000 values). Based on these findings hepatosplenic CSD was diagnosed. Treatment with doxycycline 100mg 2 times/day in combination with rifampicin 600mg 1 time/day was initiated for 6 weeks. In June 2015, the patient clinically deteriorated when suddenly complaints of undulating fever, increased fatigue and night sweats reappeared. He presented with progressive enlargement of bilateral axillar adenopathy. Integrated PET-CT scan demonstrated progressive abdominal disease with liver involvement, splenomegaly and new abnormalities of the pancreatic corpus. Pathological laboratory values were obtained for C- reactive protein : 133 mg/L ; normal < 5 mg/L, ALP : 151 U/L and ferritin : 406 μg/L ; normal < 400 μg/L. *Bartonella* serology titers remained stable compared to previous results. Histopathologically, the biopsy of the liver lobe demonstrated granulomatous CD68+ inflammation with central cell-poor necrosis. Microbiological cultures remained negative. PCR-testing of the liver tissue was strongly positive (Ct-value : 26.6) and confirmed the diagnosis of persistent CSD. Molecular testing of the biopsies for malignant hematological disorders excluded any other underlying pathology. A third generation cephalosporin (ceftriaxone 2 g/day) and gentamicin (5 mg/kg) were associated to his current treatment (doxycycline 100mg 2 times/day plus rifampicin 600mg 1 time/day) until complete cure. Further immunological follow up lead to the definite exclusion of underlying immunodeficiency.

Discussion

CSD is the most common human infection caused by *Bartonella henselae*, a small pleomorphic fastidious facultative Gram-negative intracellular coccobacillary micro-organism difficult to culture. The clinical presentation of *Bartonella henselae* infections can be diverse and partially depends on the immunologic state of the patient. In immunocompetent patients, CSD remains mainly limited to a localized, prominent regional lymphadenopathy for two weeks after inoculation and can persist for several weeks with consequent lifelong immunity. Involved lymph nodes are usually painless with often overlying skin erythema. Systemically, most patients experience fever, malaise, anorexia, fatigue, generalized aches, and headache. A history of a cat contact occurs in 95% of cases, and a primary inoculation lesion (skin, eye granuloma, mucous membrane) occurs in 61% of patients (1). Atypical systemic manifestations are observed in about 10% of all *B. henselae* infections. These are more frequent in children and immunocompromised patients (e.g. : HIV seropositivity, post solid organ transplantation, neoplasm) (4). Several organ systems can be involved and in rare cases *B. henselae* is able to generate vascular proliferative lesions, neurologic or cardiac disease and osteomyelitis (Table 2).

Cat-scratch disease is usually suspected based upon a combination of clinical presentation and a recent cat contact. The diagnosis of CSD infection must rely on the combination of epidemiological, serological, clinical, histological, and bacteriological criteria. Unfortunately, there is no diagnostic gold standard. Margileth et al. proposed following diagnostic criteria for CSD infection (presence of at least 3 mandatory) : 1. Cat or flea contact regardless of presence of inoculation site, 2. Negative serology for other causes of adenopathy, sterile pus aspirated from a node, a positive PCR assay, and/or liver/spleen lesions seen on CT scan, 3. Positive enzyme

Table 1. — **Possible presentations of CSD or B. henselae infection**

Typical presentation
▪ Skin inoculum (scratch/bite of cat or arthropod sting) ▪ Regional lymphadenopathy (possible abcedation)
Atypical – disseminated presentation
▪ Bacteremia: persisting or recurrent fever ▪ Ocular: Parinaud's oculoglandular syndrome, optic neuritis and papillitis, uveitis ▪ Dermal: erythema multiforme, erythema nodosum, purpura ▪ Granuloma or abscess formation: liver, spleen, lungs… ▪ Vasculoproliferative lesions: bacillary angiomatosis, peliosis hepatis ▪ Cardial: endocarditis, myocarditis ▪ Neurologic: encephalitis, meningitis, myelitis, radiculitis, peripheral neuropathy ▪ Musculoskeletal: myalgia, arthropathy, tendinopathy, osteomyelitis

immunoassay or IFA assay with a titer ratio of ≥ 1 :64, and 4. Biopsy showing granulomatous inflammation consistent with CSD or a positive Wartin-Starry (WS) stain (1). With WS silver stain, they can be seen singly, in small clumps, or chains in necrotic foci, but one needs good material to visualize these bacteria. In our case, histopathological examination with an adapted silver staining (Steiner) was not contributive and may lack analytical sensitivity compared to PCR analysis, even on deep tissue specimen. Our patient fulfilled all criteria. Serology is the best initial screening test and can be performed by IFA or by enzyme linked sorbent assay (ELISA). Determination of both IgG and IgM is of key importance. However, the percentage of the general population that has a positive serologic test varies widely, appearing to be higher in cat owners (5). An IgG titer of 1/320 or 1/1000 without presence of IgM mainly indicates old infections, while an IgG titer >1/1000, with or without presence of IgM is associated with recent and active infections. PCR can confirm serologic testing and can be performed on different tissue or fluids. Specificity is very high, but the analytical sensitivity is discussable and depends strongly on the tested specimen (6).

The incidence of *Bartonella* infections is difficult to establish, as there is no mandatory registration and many cases of *Bartonella* infections are not recognized or treated on an outpatient basis. In Belgium, the evaluated incidence (based on data from UCL 1993-2001) is 1.98/100.000. These findings, are comparable with those of the United States : 0.77-0.86/100.000 (7).

The therapeutic approach to CSD infection varies on the clinical manifestations and known immune status of the patient. In general, patients should be reassured that the adenopathy is benign and that it will spontaneously subside within 2 to 4 months. Immunocompetent patients with mild to moderate localized symptoms require only symptomatic supportive treatment since symptoms spontaneously disappear. If antibiotic therapy is initiated for moderate to severely ill patients azithromycin or a combination of rifampicin and doxycycline may be effective (2,3). In the most severe forms of the disease or in immunocompromised patients, a combination of trimethoprim-sulfamethoxazole with rifampicin or gentamicin, a fluoroquinolone or a third-generation cephalosporin have shown to be effective (8,9). In our case the patient was initially treated with doxycycline in combination with rifampicin. Based on his acute clinical deterioration three months after initial admission despite reliable therapeutic compliance, a third generation cephalosporin and aminoglycoside were associated. CSD can cause a diagnostic and therapeutic challenge when facing atypical, disseminated disease manifestations. Suspicion should be raised when there is a history of cat contact and a regional lymphadenopathy present at clinical examination. In rare cases, as for the one described above, the disease can be disguised as a systemic granulomatous disease.

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