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Case Report

Bartonella henselae infection presenting with a picture of adult-onset Still's disease

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SUMMARY

We report a patient with a clinical picture of suggestive for adult-onset Still's Disease (ASOD) due to *Bartonella* infection. A 42-year-old immunocompetent man was admitted with fever, rash, arthralgia and sore throat. As his clinical picture suggested ASOD except unusual skin manifestation, we treated him on steroid and ibuprofen. His fever and constitutional symptoms responded immediately within 24 hrs of commencing therapy, yet rash and leukocytosis remained. Meanwhile, *Bartonella* infection was proved by culture of bone marrow. Minocyclin treatment started combined with hydroxychloroquine sulfate and the patient discharged with overall improvement.

1. Introduction

Bartonella henselae is a small, aerobic, intracellular Gram-negative pleomorphic bacillus. Cats are the major reservoir, with up to half of domestic cats having antibodies. Once transmitted to humans via cat saliva or the scratch of a cat, *B. henselae* invades CD34+ hematopoietic progenitor cells, resulting in its intracellular presence and replication in differentiated erythroid cells.[1] In immunocompetent individuals, the response to infection with *B. henselae* is suppurative, producing a granulomatous disease.[2]

The most common manifestation of *B. henselae* infection is cat scratch disease (CSD). Typical CSD is characterized by low-grade fever and tender unilateral regional lymphadenopathy. In the majority of cases there is a history of direct cat contact. The disease course is often mild and self-limiting, leaving the incidence underestimated.

The case of an immunocompetent man presenting with autoimmune features suggestive of adult-onset Still's disease (AOSD) is described herein. Neither a history of cat contact nor granulomatous lymphadenopathy was found. During work-up of fever of unknown origin (FUO), a Bartonella infection was confirmed by PCR of the bone marrow.

2. Case report

A 42-year-old man was referred to the emergency medical center of Inha University Hospital complaining of fever and an urticarial rash of 2-week duration. He also had a sore throat, arthralgia, and a cough, which had shown no improvement following 1 week of medications at a local clinic. His past medical history was unremarkable except for the treatment of gastric ulcer 20 years ago. There was no history of travel, pet contact, or allergy. His family history was negative for autoimmune conditions.

The patient's initial blood pressure was 110/70 mmHg, pulse was 88 beats per minute, respiratory rate was 18 breaths per minute, and temperature was 38.9 °C. He showed pruritic erythematous eruptions on both arms and legs and trunk. Ophthalmological and otorhinolaryngological examinations, including fundoscopy of the eyes, were unremarkable. His chest was clear without murmurs or crackles. No organomegaly or lymphadenopathy was found. Swelling and tenderness of the joints of both hands was noted.

Laboratory studies disclosed the following values: leukocyte count of 19.26×10^9 cells/l with 83% neutrophils, hemoglobin of

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12.9 g/dl, platelet count of 138×10^9 cells/l, erythrocyte sedimentation rate (ESR) of 25 mm/h, C-reactive protein (CRP) level of 12.86 mg/dl, aspartate aminotransferase (AST) of 212 IU/l, alanine aminotransferase (ALT) of 246 IU/l, alkaline phosphatase (ALP) of 736 IU/l, lactate dehydrogenase (LDH) of 605 IU/l, total bilirubin of 0.3 mg/dl, and creatine phosphokinase (CPK) of 636 IU/l. The Venereal Disease Research Laboratory (VDRL) test, HIV testing, and serology for viral hepatitis were all negative. Computed tomography of the thorax and abdomen revealed borderline splenomegaly and a small right supraclavicular lymph node. There were no abnormal findings for the liver or lungs. A bone scan showed active joint lesions in both shoulders, knees, wrists, and ankles, and in the small joints of both hands and feet. A positron emission tomography (PET) scan showed abnormal hypermetabolic lesions in multiple lymph nodes and revealed hypersplenism and bone marrow expansion as well. Biopsies of the skin, liver, bone marrow, and cervical lymph node were performed over the clinical course.

Upon admission, broad spectrum antibiotics were started, including levofloxacin 750 g and ceftriaxone 2 g daily, however the patient showed no response. He was switched to doxycycline on day 10 of hospitalization, but his rash became aggravated after 2 days. Azithromycin (500 mg/day) was substituted resulting in a partial response, with a transient improvement in his fever and rash. However, the azithromycin also had to be stopped on the suspicion of side effects, due to the recurring fever and rash combined with eosinophilia.

Additional laboratory values were reported: antistreptolysin O (ASO) 38 IU/ml (reference range 0–160 IU/ml), procalcitonin 0.36 ng/ml (reference range 0.00–0.50 ng/ml), angiotensin converting enzyme (ACE) 30.5 U/l (reference range 9.0–47.0 U/l), and ferritin 7604 ng/ml (reference range 30–400 ng/ml). Tests for antinuclear antibody (ANA), extractable nuclear antigens, antineutrophil cytoplasmic antibody, and rheumatoid factor (RF) were negative. Repeated cultures of blood and urine were negative. An interferon-gamma release assay for tuberculosis and serology for Brucella, Toxoplasma, parvovirus, *Orientia tsutsugamushi*, Lyme disease, and Q fever were all negative. An excisional biopsy of the cervical lymph node showed reactive lymphoid hyperplasia without granulomatous inflammation, and PCR for Bartonella on this lymph node was negative. A liver biopsy showed reactive changes, and acid-fast bacillus (AFB) staining and PCR of bone marrow for tuberculosis were negative.

It was concluded that the patient's symptoms were consistent with the Yamaguchi criteria for AOSD even though the rash was not characteristic of AOSD. The patient was started on naproxen (1000 mg/day) on day 21 and prednisolone (30 mg/day) on day 25 after the report of the skin biopsy was received, which revealed superficial perivascular and mild interface dermatitis. This resulted in the prompt resolution of his fever within 24 h and an improvement in his constitutional symptoms; however, his rash and leukocytosis showed little improvement. Hydroxychloroquine sulfate (300 mg/day) was added on the suggestion of the rheumatology department.

At the authors' institution, cell culture assays are performed routinely for all patients with FUO. The patient's bone marrow was inoculated onto a monolayer of ECV304 cells. Three weeks after inoculation, certain cytopathic effects were observed. PCR with a universal primer set targeting 16S ribosomal DNA was performed to identify the bacterium isolated; Bartonella was confirmed by sequencing.[3] Species-specific primer sets of the 16S–23S intergenic spacer region groEL and ssrA revealed that the isolate was most like the *B. henselae* Houston-1 strain (NCBI accession number **KF 419277.1**).[4–6] Also, the serum IgG titer using a *B. henselae* strain (FOCUS Diagnostics, USA) was 1:320. Minocycline (200 mg/day) was added considering the patient's history of side effects with doxycycline and azithromycin. The patient was discharged after 5 days with an overall improvement in his condition.

3. Discussion

The clinical presentation of Bartonella infection no longer encompasses the original typical description from 1950. As diagnostic techniques have improved, Bartonella has been found to be responsible for a broad range of clinical syndromes. Among them, it has been found to be related to autoimmune conditions and more widely reported in children: IgA nephritis,[7] Guillain–Barré syndrome,[8] sarcoidosis,[9] autoimmune thyroiditis,[10] Henoch–Schönlein purpura,[11] and juvenile rheumatoid arthritis.[12] Meanwhile, it appears that only a few autoimmune features associated with Bartonella infection have been reported in immunocompetent adults: transverse myelitis,[13] autoimmune hemolytic anemia,[14] and lastly, Bartonella endocarditis in a 39-year-old woman.[15] This latter case had persistent fever, an urticarial rash, and arthralgia mimicking AOSD, as in the case presented here, but the Bartonella infection was confirmed by PCR of the supraclavicular lymph node.

In the present patient, the clinical diagnosis of AOSD was first made on the basis of three major criteria (fever, arthralgia, and leukocytosis) and four minor criteria (sore throat, splenomegaly, abnormal liver function tests, and negative tests for ANA and RF) being met,[16] which is known to have a high sensitivity and specificity.[17] However, *B. henselae* was cultured from bone marrow and the serum immunofluorescent IgG titer to *B. henselae* was 1:320, which was considered evidence of current infection. Accordingly, it was concluded that the Bartonella infection had triggered the systemic AOSD-like conditions; this conclusion was drawn on the basis not only of the laboratory results, but also on the clinical course, which had shown a partial response to azithromycin and an ultimate improvement with the addition of minocycline.

As is well known, the pathogenesis of autoimmune diseases is multifactorial, including genetic and environmental factors. Numerous infectious agents have been proposed as potential inciting factors for AOSD so far, but not Bartonella.[18–20] This is the first report suggesting the possibility that *B. henselae* may in part be responsible for the development of AOSD by means of either a direct inflammatory process or 'molecular mimicry' that triggers the host's autoimmune response. Further research is necessary to determine the role of Bartonella in the pathogenesis of AOSD.

In conclusion, it is suggested that AOSD-like autoimmune pictures should be added to the clinical syndromes of Bartonella infection. Furthermore, Bartonella infection should be considered during the work-up of FUO, irrespective of exposure to cats or the presence of lymphadenopathy.[21,22] Because the broad range of clinical presentations may lead to a delayed diagnosis, early serological testing for Bartonella in the evaluation of FUO may allow a rapid diagnosis, thus avoiding unnecessary invasive investigations. Also, it is notable that PCR on the bone marrow was positive for Bartonella in the case presented, yet PCR on the blood was negative. Given that bone marrow can harbor the pathogen, as *B. henselae* invades hematopoietic progenitor cells, this may have more diagnostic value in the work-up of Bartonella infection.

Conflict of interest: No competing interest declared.

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