Bartonella Infection Associated with Systemic Juvenile Rheumatoid Arthritis

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A 4-year-old girl with systemic juvenile rheumatoid arthritis had Bartonella infection diagnosed serologically. This case suggested that Bartonella (most probably Bartonella henselae) infection may in part be responsible for the development of systemic juvenile rheumatoid arthritis.

A 4-year-old girl was referred to Tokuyama Central Hospital (Tokuyama City, Japan) because of intermittent fever (daily elevation of temperature to 38°C–40°C, followed by a rapid return to normal or subnormal levels) of 25 days’ duration. The fever had persisted in spite of the sequential administration of cefpodoxime proxetil (10 mg/kg/day for 6 days), clarithromycin (10 mg/kg/day for 4 days), cefdinir (15 mg/kg/day for 2 days), minocycline hydrochloride (5 mg/kg/day for 5 days), and imipenem (60 mg/kg/day for 7 days). Laboratory data recorded during therapy included a leukocyte count of 6.9±0.5×109 cells/L, an erythrocyte sedimentation rate of 100–150 mm/h; and a C-reactive protein level of 3–9 mg/dL.

On admission, the patient complained of mild myalgia of the legs. No other symptoms, including arthralgia, joint swellings, skin rash, and lymph node swellings, were noted. Funduscopic examination of the eyes showed no abnormality. Her general condition was moderately healthy. Laboratory studies disclosed the following values: hemoglobin, 105 g/L; hematocrit, 31.2%; red blood cell count, 4.12×1012 cells/L; platelet count, 4.65×1011 cells/L; erythrocyte sedimentation rate, 92 mm/h; total protein, 86 g/L; albumin, 39 g/L; globulin, 47 g/L; IgG, 3198 mg/dL; IgA, 155 mg/dL; IgM, 323 mg/dL; complement 3, 138.5 mg/dL; complement 4, 33.4 mg/dL; lactic dehydrogenase, 685 IU; serum ferritin, 83.0 ng/mL; negative rheumatoid factor; antinuclear antibody ratio, 1:80 (homogeneous and speckled immunofluorescence patterns); 2,5-oligoadenylate synthetase (2-5 AS), 369 pmol/dL; CD4 cells, 35.8%; CD8 cells, 30.1%; CD4/CD8 ratio, 1.19. Therefore, clinical diagnosis of systemic juvenile rheumatoid arthritis (JRA) was made on the basis of high intermittent fever, hypergammaglobulinemia, high complement titers, a high titer of 2-5 AS, and an elevated titer of antinuclear antibody (although neither skin rash nor joint manifestations were noted). Diagnosis of systemic JRA in this patient may be possible, because, in some of the patients with the systemic type of JRA, persistent spiky fever may be a cardinal sign, and the patient may have neither skin rash nor joint manifestations. Treatment with aspirin (38 mg/kg/day) was started. Her clinical condition gradually improved. Her temperature dropped on the 32d day. Aspirin therapy was discontinued on day 41.

Abdominal ultrasonography was performed on day 38 to screen the visceral organs for unknown fever; several low echoic lesions (size, 5–10 mm) without a blood supply were noted in the liver and spleen. The serum sample obtained and frozen on day 26 was measured for antibody to Bartonella henselae, because the patient received a cat scratch on her finger (and had bleeding) 1 month before the onset of illness. The inoculation site appeared normal, and no regional lymph node swelling was noted on admission. Tests done by means of the indirect fluorescence antibody (IFA) method [1, 2] yielded negative results for IgM antibody to B. henselae, whereas IgG was 1:4096. The sensitivity and specificity of our IFA method were 87% and 97.7%, respectively, although serological testing for Bartonella is not species specific. Therefore, the serological diagnosis of Bartonella infection was made on day 42 of illness. PCR analysis of peripheral blood cells by use of B. henselae-specific oligonucleotides [3] failed to detect B. henselae DNA. We concluded that Bartonella infection, most probably B. henselae infection, may have triggered her systemic rheumatoid arthritis–like condition; we came to this conclusion on the basis of a markedly high titer of IgG antibody and the presence of low echoic lesions in the liver and spleen, which suggested recent infection caused by B. henselae.

Laboratory studies recorded on day 48 disclosed the following values: C-reactive protein, 0.3 mg/dL; total protein, 78 g/L; albumin, 42 g/L; globulin, 36 g/L; IgG, 2245 mg/dL; IgA, 117 mg/dL; IgM, 288 mg/dL; antinuclear antibody ratio, 1:80;
and 2-5 AS, 84 pmol/dL. Eleven months after discharge, her condition was healthy and she had no febrile history. Low echoic lesions of the liver and spleen disappeared on ultrasonography. Laboratory studies disclosed the following values: total protein, 76 g/L; albumin, 47 g/L; globulin, 29 g/L; IgG, 1360 mg/dL; IgA, 78 mg/dL; IgM, 90 mg/dL; lactic dehydrogenase, 498 IU; and antinuclear antibody ratio, 1:80.

The clinical spectrum of *Bartonella henselae* infection varies: it ranges from classic cat scratch disease with only lymphadenopathy to severe systemic disease [4]. To our knowledge, *B. henselae* infection that presents as a systemic rheumatoid arthritis–like illness has not been reported elsewhere.

Although rheumatoid arthritis has been widely suspected to have an infectious etiology, the etiology of JRA is unknown. Two hypotheses—either an infection with an as-yet-unidentified microorganism or an autoimmune reaction to unknown stimuli or microorganisms—are frequently mentioned. Various microbial agents can cause acute and chronic rheumatoid arthritis by means of microbe-host interactions [5]. The association between infection and JRA has been suggested [6].

Our findings suggest that *B. henselae* may in part be responsible for the development of systemic JRA by means of either a direct inflammatory process or a “molecular mimicry” that triggers the host’s altered immune response to *B. henselae*. Further research is necessary to determine the role of *B. henselae* in the pathogenesis of systemic JRA.

References