Leukopenia and Thrombocytopenia in a Patient with Early Lyme Borreliosis

Lyme disease, a multisystemic infection caused by the tick-borne spirochete *Borrelia burgdorferi* [1], has recently been associated with a single case of leukopenia and thrombocytopenia [2]. We report the case of a patient with documented early Lyme borreliosis, leukopenia and thrombocytopenia, and elevated liver enzyme levels.

In August 1995 a 22-year-old man who had previously been healthy developed fever, headache, myalgia, arthralgia of the knees and elbows, conjunctivitis, fatigue, and an erythematous area on the right thigh; this lesion was ~3 cm in diameter. One week earlier he had been camping in forests in Slovenia but did not remember being bitten by a tick. Four days after the onset of symptoms, he returned to Switzerland and consulted the emergency unit of our hospital. He had not taken any medication for at least a half year and had no risk factors for HIV infection.

Physical examination revealed a temperature of 39.6°C and a 5 × 7-cm erythematous oval lesion with partial central clearing typical of erythema migrans (EM), on the lateral side of the right thigh. The lymph nodes were not enlarged, and no signs of arthritis were found. Findings of the neurological examination were normal. No electrocardiographic abnormalities were noted.

Significant laboratory values were as follows: WBC count, 2.2 × 10⁹/L (neutrophil count, 1.3 × 10⁹/L [47% band forms and 12.5% segmented cells]; 26.5% lymphocytes [lymphocyte count, 0.6 × 10⁹/L]; 11.5% monocytes; 0.5% eosinophils; and 2% basophils). Morulae were not identified on review of the peripheral blood smear. Other laboratory values were as follows: platelet count, 98 × 10⁹/L; hemoglobin, 158 g/L; erythrocyte sedimentation rate, 4 mm/h; C-reactive protein, 59 mg/L (normal level, <10 mg/L); serum aspartate aminotransferase, 96 U/L (normal level, <40 U/L); serum alanine aminotransferase, 91 U/L (normal level, <40 U/L); serum lactate dehydrogenase, 580 U/L (normal level, <460 U/L); and partial thromboplastin time, 72% (normal, 70–100%). Cultures of two blood samples drawn 1 hour apart before antibiotic treatment was started yielded no bacterial growth.

A screening test (relative fluorescence; VIDAS Lyme, bioMérieux, Marcy L’Etoile, France) was used for detecting IgG and IgM antibodies to *B. burgdorferi*. Relative fluorescence values were as follows: <0.75, negative; 0.75–1.00, borderline; and >1.00, positive. Western blot analysis was performed to confirm the diagnosis; for a positive result, a minimum of five bands, including three bands of the 93-kd antigen (p100), flagellin, p39, outer surface protein A (Osp A), and outer surface protein C (Osp C), had to be present. For a borderline result, five bands, including only two of the specified bands, had to be present. The relative fluorescence values of the screening test were 0.44 on day zero (day patient presented at hospital), 1.2 one week later, and 2.6 three weeks later. The western blot analysis on day zero showed a weakly positive reaction of serum IgM antibodies to *B. burgdorferi* (six bands showing specific reactions to flagellin, p39, and Osp C) and a borderline result for IgG antibodies (five-to-six bands showing a specific reaction to flagellin and p39).

One week later, a strongly positive reaction of IgM (10 visible bands showing a specific reaction to flagellin, Osp C, Osp A, and p39) and a weakly positive reaction of IgG (eight visible bands showing a specific reaction to flagellin, p39, and Osp C) were observed. Three weeks later, the reactions of both IgM and IgG antibodies were clearly positive (more than 10 bands were visible for each).

Serological tests for IgG antibodies to *Ehrlichia equi* (the antigen was provided by Dr. J. S. Dumler, University of Maryland, Baltimore) and *Ehrlichia phagocytophila* and for IgG and IgM antibodies to tick-borne encephalitis virus, which were performed on days 7, 21, and 90, were negative. These results are consistent with seroconversion during early Lyme borreliosis. The patient was treated with doxycycline (100 mg b.i.d.) for 3 weeks. His fever resolved 24 hours after the initiation of treatment, the EM disappeared, and all laboratory parameters became normal when treatment was stopped.

Our patient presented with fever, arthralgia, myalgia, headache, conjunctivitis, fatigue, slight hepatitis, and EM—the typical symptoms and signs of early Lyme borreliosis. Seroconversion was documented by the serological screening test and confirmed by western blot analysis. Leukopenia and thrombocytopenia have not been described in large studies of Lyme disease [4–6]. In one study [4], 24 (8%) of 314 patients with early Lyme disease who were tested had elevated leukocyte counts with shifts to the left in the differential counts. A review of the literature revealed the case of a 19-year-old woman with agranulocytosis and thrombocytopenia that were caused by infectious-toxic bone marrow damage [2]. Because EM was not present, the diagnosis of Lyme borreliosis was delayed. The levels of IgG and IgM antibodies to *B. burgdorferi* were elevated, but they dropped after she was treated with oral ampicillin. In another published case, the patient had hepatitis due to recurrent Lyme disease, which was associated with isolated thrombocytopenia [7].

Our patient, as well as the two previously described in the literature, fully recovered after receiving adequate antibiotic treatment. Hypothetically, our patient could have been infected by another tick-borne infectious agent in addition to *B. burgdorferi* [8]. *Ehrlichial* diseases in humans often cause leukopenia and thrombocytopenia [9, 10]; however, the negative serological test result nearly rules the possibility of a coinfection with an *Ehrlichia* species in our patient. These three cases show that leukopenia and thrombocytopenia can occur in both early and recurrent Lyme disease. Lyme borreliosis should therefore be added to the list of infectious diseases that can cause leukopenia and thrombocytopenia.

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The Role of Human Herpesvirus 8 and Epstein-Barr Virus in the Pathogenesis of Giant Lymph Node Hyperplasia (Castleman’s Disease)

Castleman’s disease (CD) is a rare nonneoplastic lymphoproliferative disorder of unknown etiology. Two distinct histopathologic variants of CD have been described [1]: the hyaline vascular type, presenting as a tumorlike mass in the mediastinum or retroperitoneum, and the rarer plasma cell type, typically characterized by generalized lymphadenopathy, immunologic abnormalities, and type B symptoms suggestive of a systemic viral infection. Patients with generalized CD of the plasma cell type (but not those with hyaline vascular CD) are at increased risk for Kaposi’s sarcoma (KS) and lymphomas, including Epstein-Barr virus (EBV)–associated immunoblastic lymphoma of B cells and Hodgkin’s disease [2].

Both KS and a restricted group of lymphomas in patients with AIDS have been closely linked to the presence of a B-lymphotropic gammaherpesvirus [3–5], provisionally named KSHV or human herpesvirus 8 (HHV-8) [6]. DNA sequences of this virus were also found in lymph node biopsy specimens with pathological features similar to those of CD that were obtained from HIV-infected patients, most of whom had, or subsequently had, KS [7]. In the same study, however, specific DNA sequences of HHV-8 were found in only seven of 17 biopsy specimens from HIV-negative patients with CD.

To investigate whether HHV-8 could be implicated in the pathogenesis of CD, we tested six biopsy specimens from HIV-negative patients with CD (four with the plasma cell type and two with the hyaline vascular type) by PCR analysis and Southern blot hybridization with primers and probes specific for HHV-8 [3], EBV [8], and β-globin. Lymph node biopsy specimens from 15 HIV type 1–infected drug abusers with persistent generalized lymphadenopathy and five HIV-negative patients with reactive lymphadenitis were included in the study as controls. DNA from an HHV-8-positive KS lesion and tubes without DNA [9] were used as positive and negative internal controls, respectively. None of the patients had, or subsequently had, KS or lymphoma in the year following biopsy.

Lymph node samples and controls were processed in parallel according to the protocol of a 35-cycle PCR amplification starting with 500 ng of DNA obtained by proteinase K digestion, phenol-chloroform extraction, and ethanol precipitation. Strict measures were followed throughout the entire procedure to monitor the occurrence of false-positive results [10].

DNA sequences of HHV-8 were detected by PCR analysis in all biopsy specimens from patients with plasma cell CD, while both biopsy specimens from patients with hyaline vascular CD and control lymph node biopsy specimens were negative. By contrast, EBV was found in only two biopsy specimens from patients with plasma cell CD and two biopsy specimens from HIV-infected patients with persistent generalized lymphadenopathy; all other biopsy specimens were negative. By limiting dilution, semiquantitative PCR analysis revealed striking differences in the HHV-8 and EBV loads in patients with plasma cell CD. In particular, Figure 1. Results of limiting dilution semiquantitative PCR analysis of DNA extracted from patients with the plasma cell type (cases 1 and 4) and the hyaline vascular type (case 5) of Castleman’s disease.

Note the strong positivity for human herpesvirus 8 (HHV-8) in both cases of plasma cell Castleman’s disease, as opposed to Epstein-Barr virus (EBV), which is present in only case 4. Before PCR analysis, DNA was serially diluted 10-fold from 500 ng to 0.05 ng. Amplimers were performed with specific primers for human β-globin, EBV [8], and HHV-8 [3], as described previously. Amplimers were analyzed on 1.5% agarose gels, transferred onto nylon membranes, and hybridized with 32P-labeled oligomer probes.