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LONGTERM DECREASE IN THE CD57 LYMPHOCYTE SUBSET IN A PATIENT WITH CHRONIC LYME DISEASE

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Abstract: Lyme disease is a tickborne illness caused by the spirochete *Borrelia burgdorferi*. In a previous report we described a decrease in the CD57 lymphocyte subset in patients with chronic Lyme disease. We have now identified a patient with chronic relapsing and remitting symptoms of Lyme disease who had decreased levels of CD57 lymphocytes over 10 years. This observation represents the longest duration of an immunologic abnormality ever documented in chronic Lyme disease. The CD57 lymphocyte subset appears to be a useful marker of longterm infection with the Lyme disease spirochete.

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INTRODUCTION

Lyme disease is the most common tickborne illness in the world today [1, 2]. Although acute infection with the spirochete *Borrelia burgdorferi*, the principal agent of Lyme disease, responds to prompt treatment with antibiotics, failure to treat the infection may result in a chronic debilitating illness that is difficult to manage. Patients with chronic Lyme disease may have prolonged musculoskeletal or neurologic symptoms that cause significant morbidity. Studies in animals and humans with Lyme disease have shown persistence of spirochete DNA in various tissues, even after appropriate antibiotic therapy [2, 3, 4].

Recently, we identified a selective lymphocyte subset abnormality in patients with chronic Lyme disease. This immunologic abnormality is characterized by a decrease in the CD57 lymphocyte subset [1]. We now describe a patient with chronic relapsing and remitting symptoms of Lyme disease who was documented to have decreased levels of CD57 lymphocytes over 10 years.

CASE REPORT

A 34-year-old female cruise ship entertainer was evaluated for recurrent musculoskeletal symptoms of Lyme disease in April 2000. She had been bitten by ticks in Mendocino County, CA in 1989, but did not recall a definite erythema migrans rash. In 1991 she developed significant fatigue, headaches, myalgias and arthralgias and was initially diagnosed with chronic fatigue syndrome, but a Lyme Western blot was positive. She was treated with courses of oral doxycycline, clarithromycin and cefixime monotherapy but by 1994 was bedridden with severe fatigue, headaches and neuropathy in the extremities. She then received intravenous ceftriaxone for six months, followed by atovaquone and azithromycin in 1995, and she had a remission for two years without further antibiotic treatment. However, in 1998 she developed an erythema migrans rash on her arms accompanied by recurrent fatigue, headaches and flu-like symptoms. She had been working on cruise ships, and she denied repeated

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exposure to ticks. A Lyme Western blot was strongly positive.

Her symptoms improved after 6 months of treatment with doxycycline, but in January 2000 the symptoms recurred after antibiotics had been discontinued for six months. In April 2000 she was started on azithromycin and metronidazole, and her symptoms improved significantly. After three months she discontinued antibiotic treatment and the symptoms returned in September 2000. She then received clarithromycin and cefixime and her symptoms again improved. She has continued on these antibiotics with good control of the disease.

METHODS

Lymphocyte subset analysis was performed by flow cytometry using the Becton Dickinson Facscan (BD Biosciences, San Jose, CA, USA) in 1991 and 1995, and the Coulter XL flow cytometer (Beckman Coulter Diagnostics, Fullerton, CA, USA) in 2000, as previously described (1). Monoclonal antibodies were obtained from BD Biosciences for analysis of the following subsets: Absolute lymphocyte count; total CD3 T-cells; CD4, CD8 and CD57 T-cell subsets; CD3-negative CD56 natural killer cells; and CD3-negative CD57 lymphocytes (referred to as CD57 lymphocytes in the article).

RESULTS

The patient's clinical course was characterized by relapsing and remitting musculoskeletal and neurologic symptoms of chronic Lyme disease. She had variable responses to oral antibiotics and a sustained response to intravenous ceftriaxone. By chance she had measurements of her CD57 lymphocytes performed in 1991 and 1995 while she was taking oral and intravenous antibiotics, respectively (Tab. 1). Her CD57 levels were decreased on both occasions, although the levels were close to the normal range and probably reflected the beneficial effect of her antibiotic treatment. In April and September 2000, she had repeated CD57 lymphocyte analysis when she relapsed off antibiotics. On both occasions the CD57 lymphocyte levels were decreased. In contrast to these results, levels of total lymphocytes, total T-cells, T-cell subsets and CD56 natural killer cells were consistently normal over 10 years (data not shown). Thus, the patient had selective longterm abnormalities in her CD57 lymphocyte counts that mirrored her Lyme disease symptoms.

DISCUSSION

We recently identified a selective decrease in the CD3-negative CD57 lymphocyte subset as a marker of chronic Lyme disease [1]. In a cross-sectional study, patients with acute Lyme disease (defined as disease occurring within one month of infection) were found to have normal levels of CD57 cells, while untreated patients with chronic Lyme disease (defined as disease occurring more than 3 months after infection) were found to have decreased CD57 lymphocyte levels [1]. We have now documented a decrease in this lymphocyte subset over 10 years in conjunction with relapsing and remitting symptoms of the disease. This finding reinforces the concept that chronic Lyme disease is associated with a persistent immunologic defect that prevents the infection from being cleared by the immune system. Our observation also provides further evidence that a decrease in the CD57 subset may be a valuable marker of chronic infection with the Lyme disease spirochete.

Table 1. Clinical Course and CD57 Lymphocyte Levels in Chronic Lyme Disease Over 10 Years.

Date	Clinical Symptoms	CD57 Level (Cells/ul)*	Treatment**
10/14/91	Fatigue, headaches, musculoskeletal symptoms	53	Oral ABX
1/19/95	Partial remission	56	IV ABX
4/28/00	Relapse	47	None
9/26/00	Relapse	35	None

*Normal CD57 range, 60-360 cells/ul; **Treatment at the time test was performed. ABX, antibiotics.

CD57 lymphocytes (formerly known as Leu-7 lymphocytes) are thought to be a subset of natural killer cells [1]. This natural killer subset is downregulated by the Th-1 cytokines interferon-gamma, interleukin-2 and tumor necrosis factor-alpha. Cloned T-cells from patients with chronic Lyme disease have been shown to produce increased amounts of these Th-1 cytokines [5]. Thus, a persistent decrease in CD57 cells may represent ongoing Th-1 stimulation due to chronic infection with the Lyme disease spirochete. This immunologic hypothesis merits further study.

In summary, we have shown that chronic Lyme disease is associated with a decrease in the CD57 lymphocyte subset that may persist over 10 years. The decrease in CD57 cells appears to reflect a selective immunologic abnormality in patients with chronic *Borrelia* infection. Therapies that address this immunologic defect in conjunction with antibiotics may be useful in the treatment of chronic Lyme disease.

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