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Decreased CD57 lymphocyte subset in patients with chronic Lyme disease

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Abstract

Background: Chronic Lyme disease (LD) is a debilitating illness caused by tickborne infection with the spirochete *Borrelia burgdorferi*. Although immunologic abnormalities appear to play a role in this disease, specific immunologic markers of chronic LD have not been identified. *Methods*: We evaluated 73 patients with chronic LD for lymphocyte subset abnormalities using flow cytometry. Of these, 53 patients had predominant musculoskeletal symptoms, while 20 patients had predominant neurologic symptoms. The estimated duration of infection ranged from 3 months to 15 years, and all patients had positive serologic tests for *B. burgdorferi*. Ten patients with acute LD (infection less than 1 month) and 22 patients with acquired immunodeficiency syndrome (AIDS) served as disease controls. *Results*: All 31 chronic LD patients who were tested prior to antibiotic treatment had significantly decreased CD57 lymphocyte counts (mean, 30 ± 16 cells per μl; normal, 60–360 cells per μl, $P < 0.001$). Nineteen of 37 patients (51%) who were tested after initiating antibiotic therapy had decreased CD57 levels (mean, 66 ± 39 cells per μl), and all five patients tested after completing antibiotic treatment had normal CD57 counts (mean, 173 ± 98 cells per μl). In contrast, all 10 patients with acute LD and 82% of AIDS patients had normal CD57 levels, and the difference between these groups and the pre-treatment patients with chronic LD was significant ($P < 0.001$). Patients with chronic LD and predominant neurologic symptoms had significantly lower mean CD57 levels than patients with predominant musculoskeletal symptoms (30 ± 21 vs. 58 ± 37 cells per μl, $P = 0.002$). CD57 levels increased in chronic LD patients whose symptoms improved, while patients with refractory disease had persistently low CD57 counts. *Conclusions*: A decrease in the CD57 lymphocyte subset may be an important marker of chronic LD. Changes in the CD57 subset may be useful to monitor the response to therapy in this disease.

Keywords: Lyme disease; Lymphocyte subsets; CD57; Multiple sclerosis; Borrelia; HIV

1. Introduction

Lyme disease (LD) is the most commonly diagnosed tickborne disease in the US [1,2]. Although, this protean illness is more common in the eastern part of the country, it is rapidly becoming a nationwide problem [3,4]. Testing for LD has been hampered by the insensitivity of screening assays for the causative agent, significant inter-laboratory variation in performing serologic studies, and the variability of specific molecular biologic tests [5–7]. Thus more reliable forms of LD testing would be desirable.

Infection with *Borrelia burgdorferi*, the causative agent of LD in the US, has been characterized by acute and chronic phases. Acute LD is defined as disease occurring within 1 month of exposure to the organism, while chronic LD may evolve over months to years after the initial exposure [8]. Although acute LD often responds to antibiotic therapy, chronic LD is characterized by a variety of musculoskeletal and neurologic features that may be difficult to treat. Laboratory monitoring of the disease is currently unavailable.

Chronic LD has many features of a spirochete-induced immunologic illness [9,10]. In spite of this fact, immunologic studies of chronic LD are rare [11,12]. For many years, we have used extended lymphocyte subset testing to evaluate immunologic abnormalities in

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patients with human immunodeficiency virus (HIV) infection [13]. In preliminary testing of patients with chronic LD using this assay, we noted an unusual abnormality of a particular lymphocyte subset characterized by the CD57 marker [14]. We have now examined a cohort of chronic LD patients for this lymphocyte subset abnormality.

2. Patient population

The study was conducted in a LD referral practice in San Francisco. Seventy-three patients with chronic LD were enrolled in the study. The diagnosis of LD was made according to the surveillance criteria of the Centers for Disease Control and Prevention (CDC) [15]. Patients reported symptoms attributable to LD lasting from 3 months to 15 years. Forty-nine patients (67%) contracted LD while living in the eastern part of the US or in Europe, and 61 patients (84%) recalled one or more tickbites. Forty-five patients (62%) developed an erythema migrans-like rash of five centimeters or more followed by flu-like symptoms and a multisystemic illness that persisted over time. Twenty-one patients (29%) had a positive ELISA test for *Borrelia* species, while 59 patients (81%) had a positive *Borrelia burgdorferi* Western blot. Thirty-one patients (42%) were referred for lymphocyte subset analysis prior to the start of antibiotic therapy, while 37 patients (51%) had lymphocyte testing done after the initiation of antibiotic treatment. Five patients (7%) had initial lymphocyte testing performed after finishing antibiotic therapy. Sequential lymphocyte subset analysis was performed on 21 patients, with six patients having three or more tests over the course of treatment.

As a comparison group, ten patients with acute LD were evaluated prior to antibiotic treatment. The patients were diagnosed within one month of a tick-bite, and all ten had erythema migrans-like rashes and serologic evidence of acute *Borrelia burgdorferi* infection. In addition, 22 patients with acquired immunodeficiency syndrome (AIDS) due to HIV infection had lymphocyte subset analysis performed during the same time frame as the LD patients. All AIDS patients had a diagnosis based on CD4 T-cell counts less than 200 per μl, and 18 patients (82%) were receiving antiretroviral therapy.

Table 1
Patient characteristics[a]

Number/Sex	Mean age (years) (range)	MU/SK (%)	Neuro (%)
1. Acute LD			
5M	36 (13–52)	5 (100)	0
5F	43 (37–50)	5 (100)	0
2. Chronic LD			
28M	45 (14–71)	23 (82)	5 (18)
45F	43 (15–76)	30 (67)	15 (33)
3. AIDS			
21M	47 (21–63)		
1F	36		

[a] Characteristics of study subjects, LD, Lyme disease. MU/SK, predominant musculoskeletal symptoms. Neuro, predominant neurologic symptoms.

Antibiotic therapy for chronic LD was administered in a stepwise fashion. Patients with predominantly musculoskeletal symptoms (fixed or migratory arthropathies and/or myopathies) were initially treated with doxycycline 100 mg BID or amoxicillin 1.0 g BID orally for 3 months. If symptoms persisted, treatment was switched to a macrolide (clarithromycin 500 mg BID or azithromycin 250 mg BID) plus a cephalosporin (cefixime 400 mg BID or cefuroxime 500 mg BID) orally for 3 months. Patients with predominantly neurologic symptoms (cranial neuropathies, meningitis, encephalitis, and/or unexplained cognitive defects) received intravenous ceftriaxone 2.0 g daily for 3–4 months. Patients refractory to these regimens were given azithromycin 250 mg BID plus metronidazole 500 mg BID orally for 3 months. Herxheimer reactions were managed with analgesics and anti-inflammatory medications, and liver function tests were monitored repeatedly throughout the course of treatment.

3. Lymphocyte subset analysis

All lymphocyte subset testing was performed by Immunodiagnostic Laboratories, San Leandro, CA. Informed consent was obtained from all patients, and testing was carried out in a blinded fashion after routine processing of clinical samples. Lymphocyte subset analysis was done using two-color flow cytometry, as previously described [16]. Subsets included CD4, CD8 and CD8 CD57 T-cells, CD56 natural killer (NK) cells, CD3-negative CD57 cells (hereafter referred to as CD57 cells) and CD3-negative HLA DR-positive B-cells.

4. Statistical analysis

Statistical analysis of patient characteristics and lymphocyte subsets was performed using the unpaired Student t-test for parametric variables.

5. Results

Characteristics of the study subjects are shown in Table 1. Of the patients with acute LD, five were male

Table 2
CD57 Lymphocyte subset levels[a]

Patient Group	*N*	CD57 cells per μl (range)	% Low
1. Acute LD	10	116 ± 67 (60–262)[b,f,g]	0
2. Chronic LD			
A. Pre-Treatment	31	30 ± 16 (0–54)[b,c,d,e]	100
B. On Treatment	37	66 ± 39 (15–149)[c,g]	51
C. Post-Treatment	5	173 ± 98 (96–340)[d,f]	0
3. AIDS	22	103 ± 65 (33–247)[e,f]	18

[a] CD57 lymphocyte subset levels in patients with acute LD, chronic LD and AIDS. *N*, number of patients. NS, not significant. Normal CD57 range, 60-360 cells per μl.
[b] Group 1 vs. Group 2A, $P<0.001$.
[c] Group 2A vs. Group 2B, $P<0.001$.
[d] Group 2A vs. Group 2C, $P<0.001$.
[e] Group 2A vs. Group 3, $P<0.001$.
[f] Group 1 vs. Group 2C vs. Group 3, P = NS.
[g] Group 1 vs. Group 2B, $P=0.004$

Table 3
CD57 Lymphocyte subset levels[a]

Patient group	*N*	CD57 cells per μl (range)
1. MU/SK		
Pre-Treatment	21	35 ± 12 (15–55)
On Treatment	27	76 ± 39 (18–172)
Mean	48	58+37[b]
2. Neuro		
Pre-Treatment	10	20 ± 18 (0–49)
On Treatment	10	39 ± 21 (15–89)
Mean	20	30+21[b]

[a] CD57 lymphocyte subset levels in chronic LD patients according to symptom predominance. *N*, number of patients. MU/SK, predominant musculoskeletal symptoms. Neuro, predominant neurologic symptoms.
[b] $P=0.002$.

and five were female. The mean patient age was 40 years (range, 13–52 years) with a slightly older age in the female group, and all patients had predominantly musculoskeletal symptoms. Among patients with chronic LD, 28 were male and 45 were female. The mean patient age was 44 years (range, 14–76 years), with a slightly older age in the male population. Fifty-three patients (73%) had predominantly musculoskeletal symptoms, while 20 patients (27%) had predominantly neurologic symptoms. The difference in symptom predominance between male and female patients was not statistically significant. Among the AIDS patients, 21 of 22 (95%) were male, and the mean age was 47 years (range, 21–63 years). None of the AIDS patients had clinical evidence of *Borrelia burgdorferi* infection.

Results of CD57 lymphocyte subset testing according to the treatment category are shown in Table 2. The normal range for the CD57 subset was 60–360 cells per μl. All 31 chronic LD patients who were tested prior to starting antibiotic therapy had decreased CD57 levels. In patients who were tested after initiating the therapy, 51% had decreased levels of CD57 cells. All patients who were tested after finishing antibiotic treatment had normal CD57 levels. The difference between the pre-treatment and treated groups was statistically significant ($P<0.001$). In comparison, all ten patients with acute LD and 18 of the 22 AIDS patients (82%) had normal CD57 levels, and the difference between these groups and the pre-treatment chronic LD group was significant ($P<0.001$). In the AIDS patients, CD57 levels did not correlate with antiretroviral treatment (data not shown). Levels of CD4 and CD8 T-cells and B-cells were normal in all acute and chronic LD patients (data not shown). Levels of CD8 CD57 T-cells were normal in 70 of the 73 chronic LD patients (96%), and CD56 NK cell counts were normal in 66 of the 73 patients (90%) (data not shown).

Table 3 shows the results of CD57 testing according to the patient symptoms. The mean CD57 level in the group with predominant neurologic symptoms was significantly lower than the level in the patients with predominantly musculoskeletal symptoms ($P=0.002$). In both groups, mean CD57 levels were lower in the patients who were tested prior to treatment than in the patients who were already on antibiotic therapy.

Fig. 1 shows sequential CD57 testing in patients with resolving or persistent chronic LD. Patients 1 and 2 had subjective resolution of their symptoms, and these patients had normalization of their CD57 counts. Patients 3 and 4 had improved symptomatology, and these patients had increase in their CD57 counts toward normal. In contrast, patients 5 and 6 with pesistent LD had persistently decreased CD57 levels despite various antibiotic regimens. Other lymphocyte subset levels did not change in these patients (data not shown).

6. Discussion

Chronic LD is a growing problem in the US. As more ticks become infected with *Borrelia* species around the country, the incidence and spread of LD threatens to increase dramatically in the coming years. Regrettably, the diagnosis and treatment of LD has been hampered by a number of factors, including variability of disease symptoms, confusion over diagnostic criteria for LD, poorly standardized and unreproducible laboratory test results, and for physicians practicing in 'non-endemic' regions, unfamiliarity with LD presentation and treatment [17,18]. In addition, treatment recommendations have been variable and often inadequate, especially for patients with chronic infection [19,20]. In this regard, a major problem is the lack of objective therapeutic endpoints that can be used to monitor therapy in the patients with chronic disease.

Chronic LD has many features of an immunologic illness, resembling other spirochetal diseases [9,10]. In spite of this fact, systemic lymphocyte subset abnormalities in chronic LD have rarely been described [21]. By applying the extended lymphocyte subset analysis used in HIV disease to LD patients, we found a selective defect in the CD3-negative CD57 subset in patients with chronic LD (Tables 2 and 3). This abnormality in CD57 cells was specific to non-T-cells, since levels of CD8 CD57 T-cells were normal in most of our LD patients. In contrast to patients with chronic LD, all pre-treatment patients with acute LD had normal CD57 levels (Table 2). Furthermore, most HIV patients had normal CD57 levels despite significant decreases in CD4 T-cell counts (Table 2). Thus, the decrease in CD57 cells in LD appears to be related to chronic infection with the *Borrelia* spirochete rather than the non-specific result of an infectious process.

In chronic LD, CD57 levels appeared to be lower in patients with predominant neurologic symptoms than in patients with primarily musculoskeletal disease (Table 3). The reason for this difference is uncertain. The decrease in CD57 cells was consistently found in the patients prior to antibiotic treatment, and the level was shown to improve with clinically effective therapy. However, in patients with persistent LD, CD57 levels remained low (Fig. 1). Serendipedously, we were able to document decreased CD57 levels over a span of 9 years in one of our patients with chronic musculoskeletal symptoms of LD (Stricker RB, Winger EE: manuscript in preparation). Thus, the CD57 subset appears to be a useful marker for the diagnosis of chronic LD, and it may also provide an objective test to monitor therapy for the disease.

Studies of CD57 levels in neurologic and rheumatologic diseases have yielded conflicting results [22–26]. An initial report of decreased CD57 cells in multiple sclerosis [22] was not confirmed in a subsequent analysis [23]. In contrast to our findings in chronic LD, patients with rheumatoid arthritis reportedly have increased levels of CD57-bearing T-cells [24,25]. However, CD57 levels in patients with systemic lupus erythematosus and rheumatoid arthritis appear to be influenced by corticosteroid therapy, which lowers these lymphocyte counts [26]. None of our chronic LD patients were taking corticosteroids. To our knowledge, CD57 levels have not been analyzed in HIV disease prior to the current report, and levels in other infectious diseases have not been evaluated. We have found normal CD57 counts in patients with hepatitis C virus infection, primary sclerosing cholangitis, motor neuron disease or neurosarcoidosis (unpublished observation). Although chronic LD is thought to reflect an imbalance of CD4 T-cells [27], results of T-cell testing in this disease have also been conflicting [28,29]. The relationship between CD4 T-cells and CD57 cells remains poorly characterized.

The function of CD57 cells is also poorly characterized [30,31]. These cells are known to have natural killer capability, although they appear to be distinct from the CD56 NK grouping [32,33]. Indeed, most chronic LD patients with low CD57 counts in our study

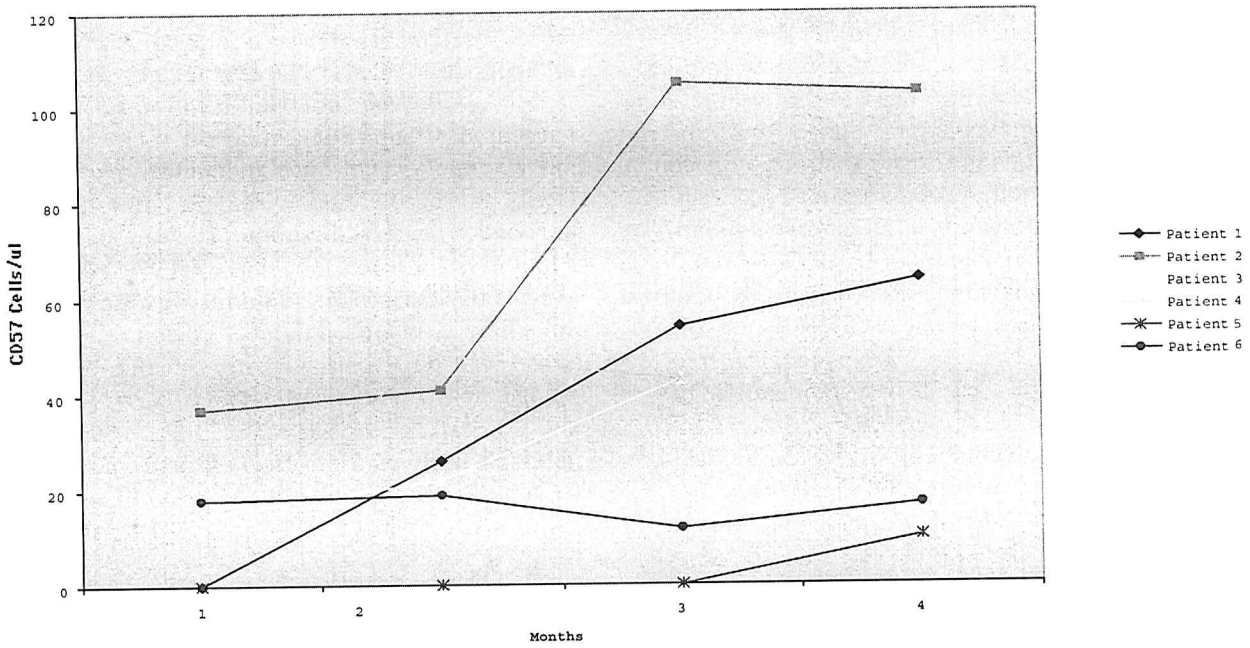

Fig. 1. Sequential CD57 lymphocyte subset testing in chronic LD patients with persistent or resolving symptoms. Patients 1–4 had clinical improvement, while Patients 5 and 6 had persistent symptoms.

had normal CD56 NK levels. Nevertheless, a decrease in CD57 cells may represent an immune defect induced by the *Borrelia* spirochete that allows infection to persist. Alternatively, it is possible that patients with a pre-existing deficiency of CD57 cells may be prone to infection with *Borrelia* species. The fact that all patients with acute LD had normal CD57 levels argues strongly against this possibility. A more likely scenario is that cytokine changes in chronic LD may influence the level of circulating lymphocytes. Cloned T-cells from patients with chronic LD have been shown to produce increased amounts of the Th1 cytokines interleukin-2, interferon-gamma and tumor necrosis factor-alpha [33], and these cytokines appear to downregulate CD57 cells (Lanier L: personal communication). The interplay among *Borrelia* infection, cytokine production and CD57 cells in chronic LD requires further study.

In summary, we have demonstrated a selective lymphocyte subset abnormality in patients with chronic LD. The decrease in CD57 cells was found in all patients prior to antibiotic therapy, and CD57 levels appeared to correlate with either clinical improvement or therapeutic failure in these patients. The role of the CD57 lymphocyte subset in the propagation of LD merits further investigation.

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