THE YALE JOURNAL OF BIOLOGY AND MEDICINE 57 (1984), 589-593

The Pathogenesis of Arthritis in Lyme Disease: Humoral Immune Responses and the Role of Intra-Articular Immune Complexes

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Received February 9, 1984

We studied 78 patients with Lyme disease to determine how immune complexes and autoantibodies are related to the development of chronic Lyme arthritis. Circulating C1q binding material was found in nearly all patients at onset of erythema chronicum migrans, the skin lesion that marks the onset of infection with the causative spirochete. In patients with only subsequent arthritis this material tended to localize to joints where it gradually increased in concentrations with greater duration of joint inflammation. In joints, its concentration correlated positively with the number of synovial fluid polymorphonuclear leukocytes. Despite the prolonged presence of putative immune complexes, rheumatoid factors could not be demonstrated. These observations suggest that phlogistic immune complexes based on spirochete antigens form locally within joints during chronic Lyme arthritis.

Lyme disease is the result of an infection with a spirochete [1,2]. The ability to identify the organism, to date its time of entry, to observe a persistent arthritis, and to treat the pre-articular phase with an effective antibiotic provide a unique opportunity to examine questions that are important in a number of major rheumatic illnesses. We have used this disease as a model for studying mechanisms of chronic joint inflammation. Because rheumatoid arthritis may be caused by an as yet elusive infectious agent, we have been particularly interested in whether Lyme arthritis requires the continued presence of the spirochete in viable form or only substances derived from it, or, alternatively, involves self-perpetuating mechanisms that the spirochete sets in motion but which remain active long after it is gone. The present study grew out of an effort to identify pathophysiological processes in Lyme arthritis that might fall into the latter category.

METHODS

Patients were diagnosed as having Lyme disease as described previously [3]. They were examined as soon as possible after the onset of erythema chronicum migrans (ECM) and at one-week to four-week intervals during symptomatic periods. At the end of a minimum of 12 months follow-up each patient was assigned to one of three categories: "skin alone" if only ECM had occurred; "arthritis" if objective arthritis had occurred with or without ECM; or "nerve or heart" if neurologic or cardiac involvement was documented. Remission was defined as no signs or symptoms for at least two weeks.

Blood and synovial fluid samples obtained during routine phlebotomies and arthrocentecies were allowed to clot at room temperature for two hours, centrifuged, and the recovered fluids were stored at −70°C until tested in the ^{125}I-C1q binding assay [4]. The amounts of radiolabeled C1q bound by patient sera were compared with that bound by a panel of normal sera: the mean and standard deviations (SD) of the binding exhibited by ten normal sera were calculated, and patient and control sera were compared in terms of multiples of this SD. Test sera with reactivity greater than 2 SD above the mean of normal were considered positive [4].

Synovial fluid white blood cell counts were performed in the clinical laboratories of the Yale-New Haven Medical Center. Sera were tested for cold reactive rheumatoid factors as described previously [5].

RESULTS

We studied 78 patients with Lyme disease, including 48 individuals with arthritis and 14 with nerve or heart involvement. The clinical features of these patients have been described previously [6]. As illustrated in Fig. 1, circulating C1q binding material was present in serum from nearly all patients tested during the first two weeks after onset of ECM. While this material usually persisted in patients with nerve or heart involvement, it tended to disappear in patients with only arthritis and was absent in patients with sustained remission.

It is important to note that detection of the C1q reactive material in these patients required careful handling of their sera. The ability of sera to bind C1q was reduced or abolished by repeated freezing or thawing or overnight exposure to room temperature. When sera were handled as described above, most of the positive patients had test results that were 2–6 SD units above the mean of normals with little variation in reactivity during storage periods of up to two years.

We previously observed that C1q binding material may be present in synovial fluid during attacks of arthritis even when it is absent from the circulation [6]. This observation suggested that the immune complexes of Lyme arthritis may be formed locally within joints. Consequently we studied 11 patients prospectively (including six who were studied serially) to determine if C1q binding material was related to the duration of joint involvement. As shown in Fig. 2, the reactivity of synovial fluid

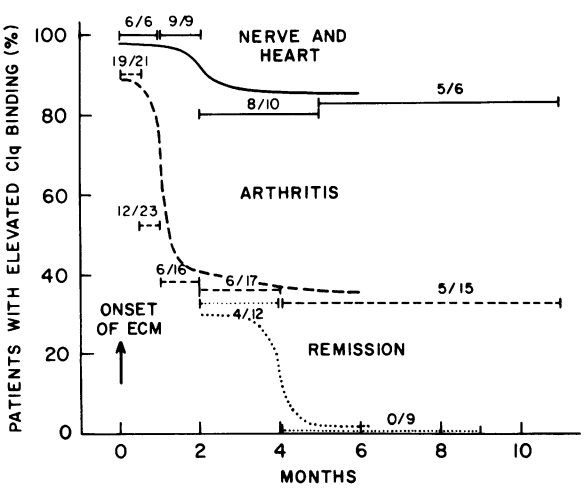

FIG. 1. Circulating immune complexes during the evolution of Lyme disease. Circulating C1q binding material is detectable in nearly all patients at onset of ECM and throughout the course of the illness in patients with nerve or heart involvement. In contrast, it tends to disappear in patients with only subsequent arthritis and is not present during sustained remission. The numerals express the actual fraction of patients with elevated C1q binding during a given time interval indicated by ⊢——⊣. The general reduction in total number of patients with time in each study group reflects the tendency for patients to be less available for study after recovery.

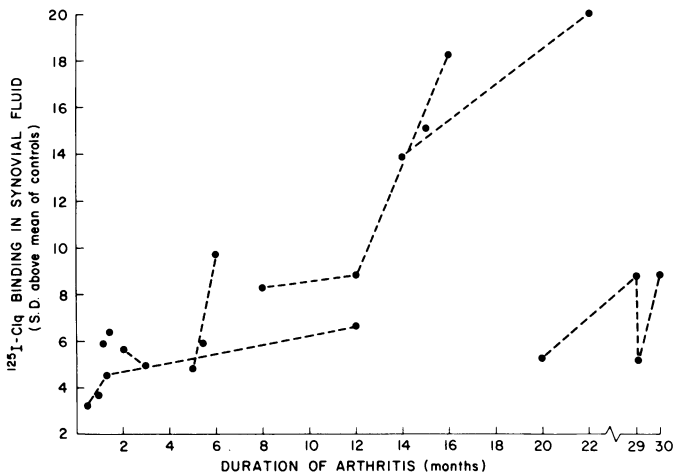

FIG. 2. Synovial fluid immune complexes during the evolution of Lyme arthritis. C1q binding material tends to increase with increasing duration of joint involvement. The dashed line connects serial studies on individual patients.

tended to rise progressively with increasing duration of arthritis. Synovial fluid C1q binding activity was found to correlate directly with the number of polymorphonuclear leukocytes in synovial fluid (Fig. 3). In contrast, no relationship was observed between C1q binding and synovial fluid content of total hemolytic complement, or complement components C3 and C4.

We observed previously that nearly all patients with Lyme disease have negative latex agglutination tests [3] and lack IgG class rheumatoid factors [4]. Moreover, tests for antinuclear antibodies have rarely been positive [7]. These observations have led us to hypothesize that autoantibodies do not appear in the course of Lyme disease. As a further test of this idea, sera from twenty patients with Lyme arthritis were tested for cold reactive rheumatoid factors using IgG coated latex particles as described in patients with mononucleosis [5]. Negative results were obtained in every case.

DISCUSSION

It is now clear that the Lyme disease spirochete is present in skin at the time of ECM and in CSF during meningoencephalitis [1]. These phases of the disease are usually accompanied by C1q binding material in the circulation. In contrast, in pa-

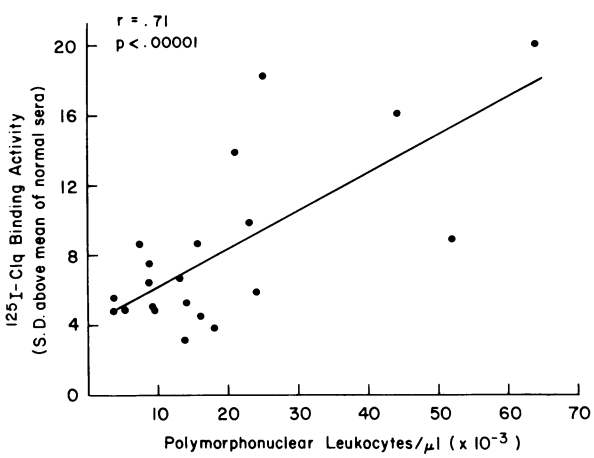

FIG. 3. Correlation of synovial fluid immune complexes with granulocytes. Granulocyte counts in synovial fluids show a positive correlation with synovial fluid C1q binding material.

tients with arthritis alone, the whereabouts of the spirochete is uncertain and immune complexes are often localized to joints, suggesting that they are being formed locally, possibly in response to spirochetal antigens [6]. It is not yet known whether antibiotic therapy universally cures chronic Lyme arthritis. When this question is answered, it should be clear whether the mechanisms responsible for the synovitis are dependent on viable spirochetes.

The present study provides further evidence that immune complexes have an active role in the pathophysiology of Lyme arthritis. They increase in concentration as the arthritis becomes more chronic and they correlate with the concentration of polymorphonuclear leukocytes in synovial fluid. In addition, aggregates of IgG and IgM have been observed in polymorphonuclear leukocytes isolated from synovial fluid of patients with Lyme disease [Newman J: unpublished data). Thus, the intraarticular immune complexes of Lyme disease appear to be involved in at least two central mechanisms of inflammation—generation of leukotactic stimuli and phagocytosis—that can potentially contribute to tissue injury.

Although Lyme disease resembles rheumatoid arthritis in the apparent intraarticular formation of immune complexes, the two diseases differ markedly with respect to the occurrence of autoantibodies. For example, in rheumatoid arthritis a variety of autoantibodies are recognized, including rheumatoid factors, antinuclear antibodies, and antibodies against collagen. Theoretically, these autoantibodies might serve to perpetuate joint inflammation even in the absence of the original causative agent [8]. It has been shown that both immune complexes and a polypeptide derived from the Fc region of IgG are powerful mitogens which can stimulate antibody production by B lymphocytes [9,10]. One can then imagine a positive feedback system in which lymphoid cells in the synovium secrete autoantibodies into the closed joint space where they bind their antigens (themselves, nuclear debris, and so on) and subsequently give rise to diffusable products that in turn stimulate yet another round of autoantibody production. It may be important that granulocyte elastase can cleave immunoglobulin to release the mitogenic Fc fragments [11].

We have been unable to detect an increased incidence of autoantibodies in Lyme disease and mechanisms such as those noted above can not be implicated in this disorder at the present time. Thus, continued immune system activity such as the characteristic prolonged elevation of IgM [12,13] may simply reflect persisting spirochetal antigens.

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