SYNOVIAL FLUID EOSINOPHILIA IN LYME DISEASE

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We describe three 14-year-old boys who developed synovial fluid eosinophilia associated with Lyme disease. One patient, with arthritis that began in 1975, had the first documented case of Lyme disease in New Jersey. Lyme disease should be considered when eosinophilia is noted on analysis of synovial fluid from patients with undiagnosed arthritis.

Eosinophils are infrequently found in synovial fluid (SF). Ropes and Bauer, in their monograph on SF changes in joint disease (1), stated that eosinophils "are not found in normal fluid." They found eosinophils in only 13 of 1,500 SF specimens from patients with various diseases (1). Amor et al examined 4,277 SF samples and found eosinophils in only 11 (2). Lemaire and colleagues found no eosinophils in any of 329 SF specimens from patients with various joint diseases (3). When eosinophils are present in SF, they rarely constitute more than 2% of the white blood cells (WBC) (4). SF eosinophilia, the presence of >2% eosinophils in joint fluid, has been reported in a limited number of disease states (Table 1). We add to that list 3 cases of Lyme disease with SF eosinophilia.

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CASE REPORTS

Patient 1. After a fall in December 1984, the patient, a 14-year-old boy who resided in eastern Delaware, experienced right knee swelling, which diminished over 2 weeks without therapy. The swelling recurred a few months later, at which time an orthopedic surgeon noted swelling of the left knee as well. Arthrocentesis revealed an "inflammatory" fluid with 69,800 WBC/mm^3. Again, the synovitis appeared to be self-limited. The boy was asymptomatic until October 1986, when he developed arthritis of the left knee and right ankle. Arthrocentesis of the left knee was performed (without SF analysis), and corticosteroid was injected. The swelling subsided for 4 days, but returned despite concurrent salicylate therapy. There was no history of tick bite, antecedent fever or rash, headache, stiff neck, facial palsy, abdominal pain, change in bowel habits, eye inflammation, or urinary symptoms.

The child was referred for rheumatologic consultation in November 1986. The only abnormalities found on physical examination at that time were swelling and effusion of the left knee and synovial

Table 1. Diseases that have been associated with synovial fluid eosinophilia

Rheumatic diseases
Rheumatoid arthritis (34,35)
Psoriatic arthritis (2)
Hypereosinophilic syndrome (36,37)
Infectious arthritides
Tuberculous arthritis (34)
Lyme disease*
Allergic disease with arthritis
Angioedema (2,38)
Atopic history (39,40)
Dermatographism (2,39,41)
Urticaria (2,38,42)
Parasitic arthritides
Ascaris lumbricoides (43)
Dracunculus medinensis (44)
Enterobius vermicularis (2)
Giardia lamblia (2)
Loa loa filariasis (45)
Strongyloides stercoralis (2)
Taenia saginata (46)
Trichuris trichura (43)
Hemorrhagic joint effusions
Adenocarcinoma metastatic to synovium (47)
Bilateral protrusio acetabuli following pelvic irradiation (48)
Postarthrography (2,11)
Postpneumarthrography (49)
Idiopathic (2,50–52)

* Reported herein.

thickening of the right ankle. Radiographs of the involved joints revealed no evidence of bony erosion. Treatment with salicylates was stopped, and a regimen of tolmetin (1,200 mg/day) was begun. The result of a polyvalent immunofluorescence assay (IFA) for antibodies to *Borrelia burgdorferi* (SmithKline Bio-Science Laboratories, King of Prussia, PA) was positive, with a titer of 1:2,048. Oral antibiotic therapy with tetracycline (1,000 mg/day) was initiated.

There was no clinical improvement with this therapeutic regimen. Four days after tetracycline was begun, the child's right calf became swollen and tender. Physical examination at that time confirmed bilateral knee arthritis and bilateral popliteal cysts. He was admitted to the hospital to receive intravenous penicillin therapy. Arthrocentesis of the left knee was performed shortly after admission (Table 2) and before parenteral antibiotic therapy was begun. Serologic studies for Lyme disease were repeated and the results were again positive, with a titer of >1:8,192. Enzyme-linked immunosorbent assay (ELISA) using sonicates of whole *B burgdorferi* was performed at the clinical immunology laboratory of the Alfred I. duPont Institute, and the results were strongly positive. Other laboratory values on admission are noted in Table 3.

The knee arthritis did not change appreciably during 14 days of therapy with intravenous penicillin G (400,000 units/kg/day), and the patient developed transient synovitis of the right third metacarpophalangeal joint and the left elbow. Arthrocentesis of the left knee was repeated after 13 days of therapy (Table 2). The patient was treated for an additional 7 days with parenteral ampicillin (8 gm/day). Upon discharge, he began a 30-day course of minocycline (200 mg/day) and tolmetin (1,600 mg/day). His arthritis diminished slowly over the next 3 months, although the popliteal cyst has persisted.

Patient 2. In July 1985, patient 2, a 14-year-old boy living in Princeton, NJ, first noted a rash with a purplish center over the left pretibial area. The rash lasted 2 weeks. Shortly thereafter, he developed sore throat, fever, and cervical lymphadenopathy. Later that month, the patient experienced right knee swelling and stiffness after playing tennis for 3 hours. The swelling subsided within 2–3 days without therapeutic intervention. Over the next 2 months, he experienced recurrent episodes of self-limited bilateral knee swell-

Table 2. Synovial fluid findings in 3 patients with Lyme disease*

	Synovianalysis						
	RBC/mm^3	WBC/mm^3	% neutrophils	% lymphocytes	% monocytes	% eosinophils	Other findings
Patient 1							
11/24/86	70,000	18,100	5	0	16	79	Glucose 53 mg/dl, protein 6.1 gm/dl, culture negative
12/10/86	90,000	21,500	85	9	6	0	Culture negative
Patient 2							
9/26/85	750	16,250	11	10	45	34	Culture negative
10/17/85	666	14,208	21	14	65	0	Culture negative
Patient 3							
2/21/75	0	38,850	5	2	43	50	Negative for crystals, SF C3: serum C3 80:190

* RBC = red blood cells; WBC = white blood cells; SF = synovial fluid.

Table 3. Laboratory findings in 3 patients with Lyme disease*

	Hgb, gm/dl	WBC/ mm^3	% eosinophils	ESR, mm/hour	ANA	RF	Serum IgM, mg/dl	Cryoglobulins	Other
Patient 1	11.0	7,000	3	55	–	–	323 (56–352)	–	Immune complexes: Raji cell 235 μg AHG, 251 μg AHG (<50); C1q binding 15%, 18% (<13%); MHA-TP negative
Patient 2	14.8	7,000	3	7	–	–	212 (70–212)	ND	Monospot negative; stool ova and parasites negative; lgE 100 mg/dl (<190); MHA-TP negative
Patient 3	13.3	11,200	10	26	–	–	110 (70–212)	–	Throat/urine cultures negative; ASO 250 Todd units; antihyaluronidase 1:512; chest radiograph normal; EKG normal; heterophil negative; HBsAg negative; RPR negative

* Numbers in parentheses are normal values. Hgb = hemoglobin; WBC = white blood cells; ESR = erythrocyte sedimentation rate; ANA = antinuclear antibodies; RF = rheumatoid factor; AHG = aggregated human globulin; MHA-TP = microhemagglutination–*Treponema pallidum*; ND = not determined; ASO = antistreptolysin O; EKG = electrocardiogram; HBsAg = hepatitis B surface antigen; RPR = rapid plasma reagin.

ing. Although the patient had been camping in wooded areas near Princeton, he had no history of tick bite.

When he developed painful clicking of the right knee in September 1985, the patient was evaluated by an orthopedic surgeon. Arthrography of the right knee joint was performed and gave normal results. The next day, he developed swelling and stiffness of the contralateral knee. Arthrocentesis of the left knee yielded 40 ml of turbid, yellow fluid. Results of the SF analysis and laboratory evaluation are presented in Tables 2 and 3. Polyvalent IFA for *B burgdorferi* (SmithKline Bio-Science Laboratories) was positive, with a titer of 1:256. Arthrocentesis was repeated 3 weeks later (Table 2). The boy took tetracycline (1,000 mg/day orally) for 1 month and has had no recurrences of synovitis.

Patient 3. Patient 3, a 14-year-old male resident of East Brunswick, NJ, developed migratory arthritis several days after the onset of a mild sore throat and cough, in late January 1975. The arthritis lasted 3 weeks. Pain and swelling first involved the right first metatarsophalangeal area; this lasted less than 24 hours and disappeared without therapy. One week later, he experienced right ankle pain and swelling, which also subsided within 1 day. A brief episode of swelling of the left second proximal interphalangeal joint followed. There was no history of antecedent trauma, rash, adenopathy, stomatitis, chest or abdominal pain, eye inflammation, Raynaud's phenomenon, or genitourinary symptoms. The patient was not specifically questioned about tick bites.

One week later, he had a fever (to 101°F), and his right knee became swollen, with associated pain on motion. Salicylate therapy was initiated, and the swelling subsided within 48 hours. Subsequently, the salicylate dosage was tapered. Within 1 week, the left knee became swollen and painful. The only abnormalities noted on physical examination at that time were a grade II apical systolic ejection murmur and a swollen left knee. Arthrocentesis yielded 20 ml of cloudy, yellow fluid of poor viscosity (Table 2). Needle biopsy of the synovium revealed superficial vascular congestion, scattered lymphocytes, and diffuse infiltration with eosinophils. It also showed focal proliferation of lining cells and a few thrombosed vessels. Laboratory findings are presented in Table 3.

The patient's arthritis again resolved after the reinstitution of salicylate therapy. However, he continued to report vague knee pains, and the swelling recurred, each episode lasting for <24 hours. Eighteen months after his first symptoms, salicylates were discontinued. He had no further symptoms or signs of inflammatory joint disease. In 1986, 11 years after presentation, stored serum was tested for antibodies to *B burgdorferi* by polyvalent IFA (SmithKline Bio-Science Laboratories) and was reactive, with a titer of 1:256. Repeat testing on serum obtained in April 1986 confirmed the persistence of antibodies to *B burgdorferi*, with a titer of 1:256.

DISCUSSION

Lyme disease is caused by the spirochete *B burgdorferi* (5) and transmitted by the bite of the deer tick, *Ixodes dammini*, other ticks, deer flies, or mosquitoes (6). Oligoarticular arthritis develops in approximately 50% of untreated patients, most commonly affecting large joints, and often occurring weeks to

years after the appearance of erythema chronicum migrans (ECM), the characteristic skin eruption of early Lyme disease (7). Most episodes of Lyme arthritis last 7 days or less and tend to recur with time. Lyme arthritis in childhood frequently occurs without antecedent ECM and can be mistaken for septic arthritis, reactive synovitis, or juvenile rheumatoid arthritis (8).

The laboratory findings and clinical courses of all 3 patients reported here are entirely consistent with Lyme arthritis, and we have found no strong indication of any other explanation for their arthritis. Patient 1 presented with recurrent episodes of knee inflammation. These bouts of arthritis were managed initially with nonsteroidal antiinflammatory drugs and with intraarticular corticosteroids. Indirect IFAs for antibodies to *B burgdorferi* gave titers that were markedly elevated, and both Raji cell and C1q binding assays for circulating immune complexes repeatedly showed positive results. The patient's serologic results were diagnostic for Lyme disease; there did not appear to be any other associated disease that might account for the eosinophilia. The development of a ruptured popliteal cyst, a known sequela of Lyme arthritis (9), complicated the clinical course. The lack of significant improvement with antibiotic therapy is consistent with the observation that patients with Lyme arthritis who have received previous intrasynovial corticosteroid therapy may not respond well to parenteral antibiotics (10). SF eosinophilia was present in the absence of peripheral blood eosinophilia, at a time when the patient's arthritis was especially active.

Patient 2's course was fairly typical of childhood Lyme arthritis, in that he had an antecedent rash and experienced recurrent bouts of synovitis of the knees (8). There was no known history of tick bite, although the patient had been exposed to a wooded environment in an area of New Jersey in which Lyme disease is known to be endemic. While arthrography has been associated with the development of SF eosinophilia in the injected knee (11), there is no evidence for an association with eosinophilia in the contralateral knee or in other joints. Treatment with tetracycline has prevented further attacks of arthritis (followup 18 months).

Patient 3 presented somewhat atypically, with a true migratory arthritis. A diagnosis of rheumatic fever was considered, but was rejected after full investigation. Because his arthritis had never been adequately explained and his SF eosinophilia was similar to that of patient 2, polyvalent indirect IFA for antibodies against *B burgdorferi* was performed on serum that had been frozen for 11 years and was repeated on a recently obtained sample. These assay results were diagnostic for Lyme disease. Further questioning revealed that the patient had no history of travel to Connecticut or to other areas of southern New England and New York where Lyme disease is endemic.

The first case of ECM in New Jersey was reported to have occurred in 1978 (12); a case of a child with Lyme arthritis in New Jersey was also reported that year (13). Patient 3's case occurred at the time of the originally described cases in Lyme, CT (14), suggesting that the disease may have appeared simultaneously in two geographically distinct areas.

IFAs for antibodies to *B burgdorferi* were developed shortly after the organism was isolated from the midgut tissues of infected ticks. While not as sensitive as the ELISA, the IFA has been shown to be quite specific for Lyme borreliosis (15,16). False-positive results in the IFA have occurred in patients with other spirochetal illnesses (16), Rocky Mountain spotted fever (17), infectious mononucleosis (5), rheumatoid arthritis (16), and systemic lupus erythematosus (16). None of our patients had clinical or laboratory evidence of any of these illnesses, however. Other investigators have called attention to the variability of results of tests for Lyme disease (18). Serologic findings in patient 1 were positive both by ELISA at the Alfred I. duPont Institute and by IFA at SmithKline Bio-Science Laboratories. The assay as performed at SmithKline Bio-Science Laboratories uses a polyvalent conjugate after adsorption and dilution of patient sera with fluorescent treponemal antibody absorbent, a manipulation which assures greater specificity in both IFAs (19) and ELISAs (20).

In patients with Lyme disease, eosinophils have been found in biopsy specimens taken from the centers of ECM lesions near the original tick bite sites (21–23), as well as from the peripheries of the lesions (24). Eosinophils have also been demonstrated in a biopsy specimen of a secondary urticarial lesion (25). In guinea pigs and rabbits bitten by larvae or nymphs of the tick *I dammini*, eosinophils have been noted in biopsy specimens of primary, secondary, and tertiary skin lesions (26).

Peripheral blood eosinophilia, as seen in patient 3, has not been reported previously in Lyme disease. It has, however, been reported in 2 patients with syphilitic arthritis, another infectious arthritis of spirochetal etiology. In one of these patients, *Treponema pallidum* was isolated from the synovial fluid (27).

Circulating immune complexes have been detected in sera of patients with Lyme disease and have been found to correlate with disease activity (28). While the antigen in the immune complexes of Lyme arthritis has not been characterized, epitopes on the spirochete *B burgdorferi* are the most likely antigens. Eosinophilia has been associated with the presence of immune complexes. Peritoneal eosinophilia can be induced in guinea pigs by the intraperitoneal injection of immune complexes (29) or of antigen into previously immunized animals. These immune complexes are phagocytized by eosinophils (30,31). Human peripheral blood eosinophils have been shown to phagocytize immune complexes in vitro (31). Thus, the presence of eosinophils in the synovial fluid of our patients may be related to the presence of SF immune complexes in Lyme arthritis. The low SF C3:serum C3 ratio in patient 3 is consistent with this hypothesis, although in none of the patients were assays for immune complexes performed on SF.

IgE antibodies to *B burgdorferi* have been detected in sera of patients with Lyme disease and in SF of patients with Lyme arthritis (32). Certain populations of activated eosinophils bear surface Fc receptors for IgE (33). As an alternative hypothesis, eosinophils in the SF of our patients may be involved in IgE-dependent cytotoxicity against *B burgdorferi*.

Because the epidemiology and pathophysiology of Lyme disease have been much better characterized than those of other arthritides, the observation of synovial fluid eosinophilia in Lyme disease may lead to an understanding of the function of eosinophils in synovial inflammation. The SF eosinophilia noted in patients 1 and 2 was a self-limited phenomenon; it was not seen on repeat joint aspirations. The hypothesis that eosinophils are transiently present in the joint space while phagocytizing immune complexes, or in response to *B burgdorferi*, is suggested by the brevity of the SF eosinophilia. This brief duration may explain why SF eosinophilia has not been noted previously in Lyme arthritis. Further studies are necessary to characterize the role of eosinophils in the synovitis of Lyme arthritis. However, when eosinophilia is noted on synovial fluid analysis, Lyme disease should now be considered as part of the differential diagnosis.

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