Case Report

Systemic Lupus Erythematosus Evolving into Rheumatoid Arthritis

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ABSTRACT. We describe 3 patients who presented with clinical and serological evidence of systemic lupus erythematosus (SLE) and 10 or more years later developed for the first time clinical and serological manifestations of rheumatoid arthritis (RA). Each patient now meets the American College of Rheumatology criteria for both SLE and RA. (J Rheumatol 2006;33:188–90)

Key Indexing Terms:
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Rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) are common rheumatologic disorders. True coexistence of these 2 diseases in the same patient, however, is rare. Schur[1] first used the term "rhupus" in 1971 to describe patients with a mixture of clinical features of RA and SLE, and this entity has recently been reviewed[2]. Serological overlap between RA and SLE is well known. Up to 40% of patients with RA may exhibit antinuclear antibodies[3], and up to 35% of patients with SLE have rheumatoid factor[4]. However, patients having both clinical RA and clinical SLE by American College of Rheumatology criteria are rare.

Most of the reported cases of "rhupus" initially presented with clinical features of RA, and later developed the clinical and serological manifestations of SLE[5-7]. That deforming arthropathy and even the erosive type occurs in a subset of patients with SLE makes it difficult to classify such patients as having rhupus if they initially presented with SLE[8]. However, the presence of additional findings, such as nodules and positive serologic markers, strongly suggests the coexistence of these 2 disease entities. Recognition of these patients is important, since their therapy and outcome differ from those having SLE or RA alone. SLE patients rarely evolve into RA patients. We describe 3 patients who had SLE as the initial presentation and, after many years of disease, developed clinical and serological manifestations of RA.

CASE REPORTS

Case 1. A 29-year-old Caucasian woman presented with fatigue, facial rash, and intermittent arthralgias. On examination, she had a malar rash with nasolabial sparing, nasal septal ulcers, and synovitis that involved her proximal interphalangeal (PIP) joints, metacarpophalangeal (MCP) joints, and wrists. Her initial laboratory investigations revealed leukopenia (3500/mm^3), antinuclear antibodies (ANA) 3+ diffuse pattern, anti-double stranded DNA 65 units (Farr method), anti-Sm 1:4, anti-Ro 1:16 (immunodiffusion method), C3 53 mg/dl, and C4 < 8 mg/dl. Rheumatoid factor (RF) was negative. Radiographs of hands and feet revealed no erosions. SLE was diagnosed and she was treated with prednisone and hydroxychloroquine. Most of her symptoms were controlled, but over a period of 10 years, she gradually developed ulnar deviation, boutonniere and swan neck deformities, and had increasing joint symptoms. For many years, her hand deformities were felt to be Jaccoud's arthropathy. However, 18 years after SLE was diagnosed, radiographs revealed a small focal area of erosion involving the right triquetrum, and she developed nodules on her left thumb, right second and third fingers, and in both palms. Biopsy of these nodules revealed histopathologic changes consistent with rheumatoid nodules (Figure 1). RF and anticyclic citrullinated peptide (CCP) antibodies were negative. With increasing arthritic complaints, methotrexate (MTX) was added to her regimen, but she had poor clinical response. She was treated with leflunomide with subsequent improvement.

Case 2. A 28-year-old white woman presented to our clinic with a photosensitive facial rash and arthritis of her hands, wrists, elbows, and shoulders. She had a good response to nonsteroidal antiinflammatory drugs. Recurrence of rash prompted a skin biopsy, which was compatible with lupus. Physical examination revealed active synovitis of wrists, PIP, and MCP joints and her left knee. Her erythrocyte sedimentation rate was 78 mm/h, ANA 3+ diffuse, and anti-dsDNA antibodies 74 units. Her C3 and CH50 levels were within normal limits, but C4 was low. She had anticar-

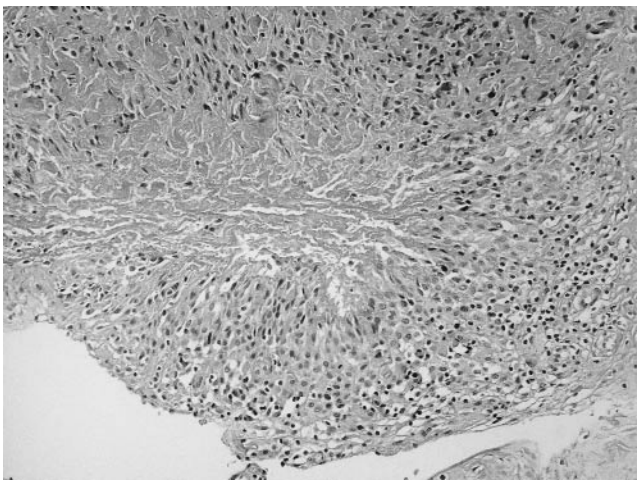

Figure 1. Patient 1: rheumatoid nodule, histopathology.

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diolipin antibodies. All other tests, such as anti-Ro, La, Sm, RNP, and RF, were negative. Radiographs of her hands showed no erosions. SLE was diagnosed and she was treated with hydroxychloroquine and prednisone. A few years later, she developed alopecia and proteinuria with pitting edema of her lower extremities, and low C3 levels. Her kidney biopsy showed diffuse proliferative glomerulonephritis, and she was treated with prednisone 60 mg per day. In subsequent visits, she had various migratory joint pains involving wrists, shoulders, knees, and PIP joints. Four years after initial presentation, she developed vertigo, facial and left arm paresthesias, and orthostatic hypotension. She also developed a petechial rash on her ankles, and was found to be thrombocytopenic. She was treated with prednisone 60 mg/day with good response. Her lupus then remained clinically silent, and she was maintained taking prednisone 5 to 10 mg/day.

Twelve years after initial presentation, she developed nodules over her right first interphalangeal joint and both elbows (Figure 2). She had synovitis of wrists, hands, and feet and significant morning stiffness. Radiographs revealed degenerative changes. Her RF, previously negative, was found to be 1:5120, with negative anti-Ro, La, Sm, and RNP antibodies. Anti-CCP antibody was present. She responded poorly to MTX.

Case 3. A 29-year-old Caucasian woman first presented with a 3-year history of livedo reticularis and migratory joint pains involving her knees, wrists, ankles, and shoulders. She had hair loss, fatigue, Raynaud's phenomenon, and significant morning stiffness. Her examination was notable for oral ulcers and joint tenderness. She had an ANA 3+ diffuse 1:64, negative anti-dsDNA antibodies, normal C3 and C4, positive direct Coombs' test, false positive VDRL, and positive anticardiolipin antibodies.

Antibodies to Ro, La, Sm, and RNP were negative. RF was negative. She had a good response to prednisone and hydroxychloroquine. A year later, she presented with pruritic rash over her forearms, which on biopsy was consistent with polymorphous light eruption. She also had an episode of pleuritic chest pain with a negative chest radiograph.

Ten years after diagnosis, most of her complaints were limited to significant arthritis of her hands, wrists, hips, and knees. These symptoms paralleled the tapering of her prednisone dose. She had findings of synovitis of MCP and PIP joints. Radiographs of her hands were normal. Twelve years after diagnosis, she developed nodules on her hands. Her RF was 1:1280 and anti-CCP antibody test was positive. She did not have a significant clinical response to MTX, azathioprine, or hydroxychloroquine.

DISCUSSION

The coexistence of 2 or more connective tissue diseases in the same person is a rare phenomenon, particularly that of RA and SLE, or rhupus. Due to the paucity of reported cases of rhupus, it has been suggested that it is merely coincidental. However, in 1987 Cohen, *et al*[7] reported 3.6% of their patients with SLE had overlapping RA, which is greater than the 1% prevalence of RA in the Caucasian population. The serological overlap between RA and SLE is well known, with up to 40% of RA patients exhibiting positive ANA[3]. Similarly, up to 35% of SLE patients have been reported to have RF[4]. However, true clinical overlap of these diseases is rare.

Figure 2. Patient 2: subcutaneous nodule.

All the reported cases of rhupus had RA as the initial presentation[5-7]. Few reported cases simultaneously presented features of both RA and SLE[6]. We describe the first patients with SLE as the presenting diagnosis.

All our patients had SLE as the initial presentation and did not develop RA until 10 or more years after SLE was diagnosed. All presented with arthralgia, which is well described as the presenting manifestation of SLE in more than 50% of cases[8,9]. Patients 2 and 3 had positive RF and anti-CCP antibodies at the time the disease changed. RF can be seen in SLE patients in up to 35% of cases[2]. However, the presence of anti-CCP antibodies has not been reported in patients with SLE. Patient 1 had deforming arthropathy with erosion. Van Vugt, *et al*[10] reported 10% of their patients with SLE (17 of 176) had deforming arthropathy. Almost half of these had Jaccoud's deformity (4.5%), and more than one-third had mild deforming arthropathy (3.4%). Only 3 out of 176 patients had deforming arthropathy with erosions (1%), which is consistent with prior reports by Dubois, *et al*[12]. Whether these patients represent a subset of SLE arthritis or the true coexistence of the 2 diseases is not clear. Our 3 patients also had nodules, which are common in RA. However, the reported occurrence of nodules in SLE is rare[13,14].

Our patients had been given disease modifying agents, other than hydroxychloroquine. There was no significant clinical response to any of these agents. It is possible that one disease, then, may modify the expression of the other, as well as its response to conventional treatment.

The pathophysiology for the coexistence of SLE and RA is not well understood. Our patients had SLE for at least 10 years before their clinical picture shifted to that of RA. They also developed RF. One possible explanation of this phenomenon is epitope spreading, which refers to the observation that one autoantibody profile may evolve into another in association with changing clinical manifestations in a single patient. This phenomenon occurs due to the fundamental differences in how B and T cells recognize antigen[14]: the T cell responds only to a small antigenic peptide fragment presented by HLA molecules on antigen-presenting cells. T cells subsequently stimulate specific B cells via cytokines to produce antibodies to the peptide fragment. In contrast, immunoglobulins recognize intact or nonprocessed antigens, and allow B cells to be able to bind them. Since B cells

are also antigen-presenting cells, they may capture and process the original intact antigen and subsequently present different peptide fragments to other T cells. Additional antibodies directed against these new epitopes may therefore be produced. As a result, the antibody response may diversify or begin "epitope spreading."

Failure in the tightly regulated process of apoptosis could be another possibility. Defects in apoptosis, or programmed cell death, have been a mechanism proposed for the pathophysiology of both SLE[15] and RA[16]. Even more important is the process of eliminating the products of apoptosis, the apoptotic bodies, which contain numerous potential antigenic materials. These apoptotic bodies are normally cleared in a rapid and efficient fashion by the macrophages. Defects in this clearance mechanism could lead to accumulation of cellular fragments in various tissues. These autoantigens may then encounter dendritic cells, which leads to the production of autoreactive T cells. B cells will be activated in the process, and will differentiate to memory or plasma cells, which may produce autoantibodies against these fragments. All of these could lead to the development of a clinical disease.

We describe 3 patients who initially presented with clinical and serological features consistent with SLE, which subsequently changed to those of RA many years after the initial presentation.

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