

Erosive arthropathy: clinical variance in lupus erythematosus and association with anti-CCP case series and review of the literature

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Abstract

Objective

To describe the occurrence of erosive arthropathy in systemic lupus erythematosus (SLE) and its relationship to anti-CCP antibodies.

Methods

Retrospective medical record review of a case series of five female patients with SLE and erosive arthropathies.

Results

The initial disease presentation in all patients was a polyarthritis. Anti-CCP antibodies were detected in 4 out of 5 (80%) patients, 2 of whom had a positive rheumatoid factor.

Conclusion

Erosive arthritis was strongly associated with the presence of anti-CCP antibodies in these patients with SLE, who presented with polyarthritis. Anti-CCP in patients with SLE may be a marker of a more severe joint disease.

Key words

Systemic lupus erythematosus, erosive arthritis, rhupus, anti-CCP.

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Introduction

Like rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) is one of the most common inflammatory autoimmune disorders. SLE is characterized by systemic involvement and presence of autoantibodies including antinuclear antibody (ANA) and anti-DNA. The arthropathy of these conditions has variable expression, whereby in RA, it is generally symmetric, aggressive, progressive, and erosive, often within the first three years of disease, and principally affects the small joints including those of the hands and feet, while in SLE, only a minority of patients develop erosions in the small joints during the course of their disease (1, 2).

SLE may be difficult to differentiate from RA when its initial manifestation is articular involvement, as arthritis is one of the most common manifestations of lupus and usually appears early. Kaposi had already suggested that articular involvement in SLE was also one of the most serious manifestations of SLE (3), and Ossler described articular involvement in detail in patients with SLE including involvement of the small joints of the hands as well as ankles and wrists (4).

The severity of articular involvement in SLE is variable, ranging from minor arthralgias to severe deforming arthritis. It may be transitory, migratory, and reversible, while much less commonly its course is chronic with deforming arthritis affecting principally the hands, feet, and knees (5-7).

Erosive arthritis in SLE is unusual and may be present in about 5 percent of patients and is usually deforming (6-9). While nonerosive arthritis is much more common, even nonerosive arthritis can cause extreme joint capsule and tendon laxity and periarticular fibrosis in the hands and feet, which resembles the arthritis of RA and is known as Jaccoud's arthritis (5, 6, 10, 11). This form of arthritis is frequently associated with sicca syndrome and less frequently with cutaneous and renal involvement (7, 12).

Risk factors and pathogenic mechanisms associated with the development of erosive arthritis in SLE are poorly

understood. Many of these patients with deforming erosive arthritis have a positive rheumatoid factor and antibodies to anti-RA33, which are typical of erosive RA13 and may be present in this group of SLE patients in between 20 and 70 percent in the published literature (9, 14, 15). The anticyclic citrullinated peptide (anti-CCP) is considered to have high specificity and moderate sensitivity for RA and is increasingly utilized in the diagnosis of this disease (16-18). There are no reports of its possible utility as a prognostic marker in the development of lupus arthropathy (whether erosive or nonerosive). A few studies to date have suggested that anti-CCP antibody may have a lower prevalence (about 20 percent) among patients with SLE, and that it may be useful in the differential diagnosis between the two entities (14, 19-21). In our experience, erosive arthritis in patients with SLE occurs in a subgroup of patients whose disease generally begins with an inflammatory arthropathy and later in the natural course of the disease and typical immunologic abnormalities of lupus, although the factors governing the development of these manifestations are unknown (22, 23, 34).

We report a series of five patients with SLE who developed erosive arthritis resembling rheumatoid arthritis and discuss several historical, clinical, and serologic aspects of these cases and their possible association with anti-CCP.

Case 1

A fifty-two-year-old female with symmetric polyarthritis involving small and large joints of 15 years' duration. Joint involvement included the wrists, metacarpal phalangeal joints (MCPs), proximal interphalangeal joints (PIPs), knees, and feet with morning stiffness of 30 to 60 minutes. The patient was initially diagnosed with rheumatoid arthritis and treated with methotrexate, 10 mg per week, and methylprednisolone, 40 mg per day, with improvement. Two years after disease onset, the patient presented with acute fever, malar rash, photosensitivity, oral ulcers, sicca symptoms, Raynaud's, and dyspnea on exertion. The patient was first hospital-

ized on our service with progressive dyspnea, deteriorating to functional class 4, and generalized edema, pallor, left-sided pleuritic chest pain, and lower extremity purpura (Fig. 1).

On physical examination, the patient was orthopneic, tachypneic, pale, had jugular venous distention of grade 3 at 45 degrees with a holosystolic murmur (grade 3/6) over the mitral region radiating to the medial axillary line with S2, inspiratory crackles, fremitus, and diminished breath sounds in both lung bases. The liver was palpable at 5 cm below the right costal margin. There was marked edema in the lower extremities and abdominal wall with acute and chronic synovitis of the elbows, wrists, MCPs, PIPs, knees, and feet.

Global cardiac failure with SLE related cardiomyopathy was suspected. The initial laboratory results supported this diagnosis. The patient had a normocytic anemia, leukopenia and lymphopenia, positive direct Coombs, normal urine sediment, elevated sedimentation rate, positive ANA (1:5120, homogeneous pattern), anti-DNA (1:320), and anti-Ro, elevated at 127.4 (normal < 25 U). Anti-SM, La, and RNP were negative; complements C3 and C4 were normal, rheumatoid factor was negative, and anti-CCP antibody was elevated at 147 U (normal: < 20 U). Anticardiolipin antibody IgG was elevated at 73.4, lipoglycoprotein was elevated, IgM was normal, while B2 glycoprotein 1, IgG, and IgM were negative, as were the lupus anticoagulant and cryoglobulins. Chest radiograph revealed cardiomegaly with left ventricular enlargement and evidence of pulmonary hypertension and a left pleural effusion (Fig. 2). Radiographs of the hands, feet, and knees revealed diffuse osteopenia and joint-space narrowing in the wrists, MCPs, and PIPs with multiple erosions (Fig. 3).

A diagnosis of SLE was based on the myocardial disease, valvular disease, hemolytic anemia, vasculitis, and erosive rheumatoid arthritis. Initial treatment was with pulse methylprednisolone and cyclophosphamide at conventional doses, resulting in clinical improvement five days after beginning therapy. The cytopenias resolved, acute-

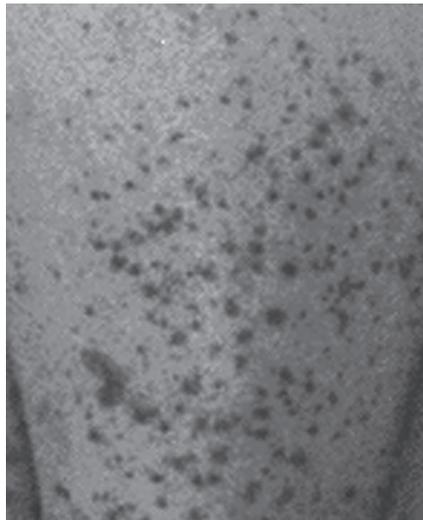


Fig. 1. Multiple purpuric papules on the thigh.



Fig. 2. Marked cardiomegaly with evidence of pulmonary hypertension and left-sided pleural effusion.

phase reactants returned to normal, and the articular symptoms resolved within two weeks. A transesophageal echocardiogram, at that point, revealed adequate left ventricular function, increase in right sided pressures, and minimal mitral insufficiency without evidence of vegetations, intracardiac

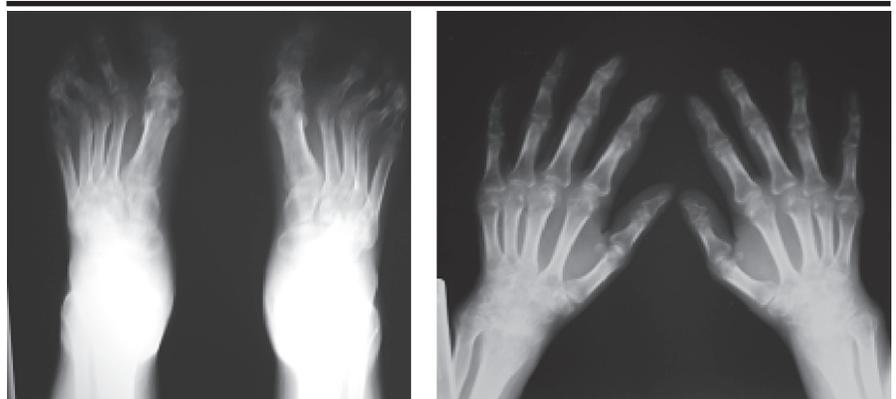


Fig. 3. A. Periarticular osteopenia, B: Joint space narrowing and erosions in Erosions and subluxations of the MTPs the MTPs and PIPs of the hands.

thrombi, or pulmonary hypertension.

Case 2

A forty-seven-year-old woman with a six-year history of symmetric polyarthritis of the small joints of the hands and feet, morning stiffness, swan-neck deformities and reducible ulnar deviation, Raynaud's, sicca symptoms, dysphagia for solids, malar rash, photosensitivity, and class 2 dyspnea of recent onset, who was initially treated with prednisone, methotrexate, and folic acid for a diagnosis of rheumatoid arthritis at another institution. On evaluation, the patient had leukopenia, positive ANA at 1:22,560 with homogeneous pattern, positive anti-Ro at 56 U (normal < 25 U), positive anti-RNP at 86 U (normal < 25 U), positive anti-double-stranded DNA, 1:40, positive anti-CCP antibody at 110 U, and negative rheumatoid factor. Radiographs of the hands and feet revealed juxtaarticular osteopenia, joint-space narrowing, subluxation, and erosions of the carpus and MCPs. A diagnosis of SLE with deforming erosive arthropathy was made.

Case 3

A thirty-six-year-old woman with a five-year history of symmetric polyarthritis of the hands, feet, and knees, initially accompanied by alopecia and xerostomia as well as positive rheumatoid factor (120 U; normal < 60 U), positive ANA of 1:640, homogeneous pattern, initially without other disease manifestations. Initial radiographs of the hands and feet demonstrated juxtaarticular

osteopenia, joint-space narrowing in the MCPs and PIPs, and erosions in the carpus and MCPs. Therapy was initiated with glucocorticosteroids, anti-malarials and methotrexate for a diagnosis of RA. The patient subsequently developed a malar rash, exacerbation of the arthritis, and persistent alopecia. Further laboratory tests demonstrated a normocytic, normochromic anemia with leukopenia, microalbuminuria (280 mg/24 hrs), normal creatinine clearance (95.8 mg/min), detectable rheumatoid factor (30 U), positive ANA with homogeneous pattern (1:320), and positive anti-DNA (1:40) with negative anti-Ro, anti-La, SM, and RNP, normal C3 and C4 complement, but positive anti-CCP antibody (148.3 U). The patient was diagnosed with SLE and erosive arthritis.

Case 4

A thirty-two-year-old female who presented with a six-year history of symmetric polyarthritis of the shoulders, wrists, MCPs, PIPs, knees, and feet, as well as Raynaud's, alopecia, generalized myalgia, diagnosed at an outside institution with undifferentiated connective tissue disease and treated with prednisone, 10 mg per day, aspirin, 100 mg per day, and nifedipine, 30 mg per day. Six months prior to presentation, she was seen urgently at another institution for an episode of thoracic pain and dry cough accompanied by dyspnea and was diagnosed with pericarditis, confirmed on echocardiogram. The prednisone dose was increased, and nonsteroidal anti-inflammatory drugs were prescribed. At the time of referral, she had photosensitivity, and a recent onset malar rash but had no other evidence of active inflammation. A presumptive diagnosis of SLE was made, and the patient was treated initially with hydroxychloroquine, 200 mg per day, and methotrexate, 7.5 mg per week. Laboratory examination revealed leukopenia and normochromic, normocytic anemia, normal urinary sediment and creatinine clearance, ANA of 1:5120 speckled pattern, and anti-DNA of 1:80. Rheumatoid factor was negative, and complements C3 and C4 were normal, as were anticardiolipin antibodies, IgG and IgM, anti-Ro,

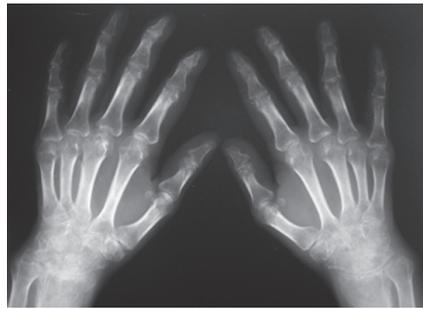


Fig. 4. Soft tissue swelling, periarticular osteopenia, joint space narrowing and erosions in the PIPs, MCPs, and destructive arthritis of the wrists.

anti-La, anti-RNP, and anti-Smith (Sm) antibodies, while the anti-CCP antibody was 12.9 U. Radiographs of the hands and feet demonstrated diffuse osteopenia, joint-space narrowing in the MCPs and PIPs, and multiple erosions (Fig. 4). A diagnosis of SLE with secondary erosive arthritis was made.

Case 5

A fifty-five-year-old female with a 16-year history of polyarthritis of the hands, knees, and feet, morning stiffness of one hour, with positive rheu-

matoid factor (132 U) and a positive ANA at 1:640 (homogeneous pattern). Radiographs of the hands revealed juxta-articular osteopenia, joint-space narrowing in the MCPs and PIPs, and carpal destruction

An initial diagnosis of RA had been made, and treatment was initiated with hydroxychloroquine at a dose of 200 mg per day, methotrexate at 7.5 mg per week, and nonsteroidal anti-inflammatory agents. Treatment response was poor, and the patient subsequently developed photosensitivity, alopecia, xerostomia without xerophthalmia, and active urinary sediment with a protein of 900 mg/24 hours, large numbers of red blood cells in urine, and marked microscopic hematuria and leukocyturia, for which prednisone, 30 mg per day, was prescribed.

Follow-up laboratory evaluation demonstrated leukopenia and normalization of creatinine clearance and low-grade proteinuria (0.8 gm/24 hours). The ANA was positive at 1:1280 (homogeneous pattern) with negative anti-DNA and negative Ro, negative La, negative Sm, and negative RNP,

Table I. Demographic, serologic and radiologic features of patients with erosive lupus arthropathy.

Feature	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Sex	Female	Female	Female	Female	Female
Age (years)	52	47	36	32	55
Disease duration (years)	15	6	5	6	16
Rheumatoid factor (Units < 60 = absent)	absent	absent	120 U	absent	132 U
Antinuclear antibody (ANA)	1:5120	1:2560	1:320	1:5120	1:1280
Pattern	Homogeneous	Homogeneous	Homogenous	Speckled	Homogenous
Anti-DNA titer	1:320	1:40	1:80	1:320	absent
Anti-Ro (Units; < 25 = absent)	127.4U	56U	absent	absent	absent
Anti-La	absent	absent	absent	absent	absent
Anti-Sm	absent	absent	absent	absent	absent
Anti-RNP (<25 = absent)	absent	86U	absent	absent	absent
Complement C3	normal	normal	normal	normal	normal
Complement C4	Normal	normal	normal	normal	normal
Anti-cyclic citrullinated peptide (Units; < 20 = negative)	147U	110U	148.3U	12.9U	115.5U
Radiographic joint erosions	present	present	present	present	present

ANA testing by Hep2 (Biorad); dsDNA by indirect immunofluorescence (Seus); ENA (Sm, RNP, Ro, La) by ELISA (Innova); CCP by ELISA (Innova, second generation kit).

Table II. Diagnostic criteria of patients with systemic lupus erythematosus and erosive arthritis.

Classification criterion	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Malar rash	+	+	+	+	
Discoid rash					
Photosensitivity	+	+		+	+
Oral ulcers	+				
Arthritis	+	+	+	+	+
Serositis*	+			+	
Renal disorders**			+		+
Hematologic disorder***	+	+	+	+	+
Neurologic disorder†					
Serology**	+	+	+	+	+
Antinuclear antibody	+	+	+	+	+

*Present.

†Pleuritis.

**Persistent proteinuria of more than 0.5gr/day or more than 3+ on dipstick if not quantified, or cellular casts.

***Hemolytic anemia with reticulocytosis, or leukopenia of less than 4000 cells/10-9L or lymphopenia of less than 1500 cells/10-9L, or thrombocytopenia of less than 100,000 cells/10-9L on two or more occasions not due to medication or other causes.

•Convulsions, psychosis not explained by medication or other causes.

**Antibodies to anti-native DNA, or anti-Sm, or anti-cardiolipin antibodies.

detectable rheumatoid factor (32 U), total complement (CH50), at the lower limit of 150 U (normal, 150-250 U) and the CCP antibody was positive at 115.5 U. A renal biopsy demonstrated mesangioproliferative nephritis and positive immunofluorescent staining of the glomerular membranes with IgG and C3, consistent with stage 2 lupus glomerulonephritis. A diagnosis of SLE could be made with renal involvement and secondary erosive arthritis. The prednisone dose was increased to 60 mg per day, with resultant improvement in the patient's disease.

Discussion

The coexistence of two autoimmune inflammatory diseases in the same patient occurs with variable frequency, but certain associations are relatively rare, especially a co-occurrence of SLE and RA, which is estimated to have a prevalence of only about 0.1 to 2 percent (24, 25) and is generally termed, "Rhupus." The first report about this association was in 1960 by Toone, who described the presence of SLE cells in the serum of 15 patients with RA at a time when these cells were considered to occur exclusively in patients with SLE26. Subsequently, other authors in the 1960s and 1970s also reported on this clinical association (27-29).

A series of publications including ap-

proximately 60 cases described as "Rhupus" have been reported (24, 30-34). This condition is defined as a simultaneous presence in the same patient of erosive, symmetric polyarthritis, symptoms and signs of SLE and detection of antibodies with relatively high sensitivity and specificity for both diseases (rheumatoid factor, ANA, and anti-DNA in the same patient) (35, 36). In many of these cases, it is difficult to determine whether some of these cases are patients with SLE and erosive arthritis or RA with extraarticular manifestations or patients with mixed connective tissue disease (MCTD) or whether indeed they have Rhupus.

Panush *et al.* (24) reported on six patients who fulfilled clinical criteria established by the American College of Rheumatology (ACR) for both diseases (37, 38) from a series of 7000 patients evaluated over 11 years. The manifestations of RA in these patients included chronic, symmetric polyarthritis, morning stiffness, sub-cutaneous nodules (two patients), positive rheumatoid factor (four patients), and radiographic erosions (four patients). The manifestations of SLE in these six patients included rash (three patients), discoid lupus (two patients), photosensitivity and lupus nephritis (one patient), leukopenia or lymphopenia (four patients), hypo-complementemia

(two patients), and positive ANA (six of six patients). They established the prevalence of the coexistence of RA and SLE was estimated to be 0.09 percent, and the authors viewed their coexistence as due to chance.

Other authors including Cohen *et al.* (30), Brand *et al.* (32), Simon *et al.* (33) and Fernandez *et al.* (38) have described multiple cases of 11 patients with coexistent RA and SLE. These reports emphasize the variable interval (up to 21 years) between the appearance of the diagnostic features of the two conditions, prominence of renal involvement, as well as positive ANA and rheumatoid factor is over 90% of cases. Many had rheumatoid nodules, DNA antibodies and anti-Ro. In one series (32) HLA-DR4 was detected, and 63% had positive DR2 or DR3.

In our series, all patients were women who presented with symmetric polyarthritis of the small and large joints, which was found to be erosive on radiographs. Rheumatoid factor was present in only 40% of patients. Anti-Ro was present in 40% of patients, while 80% of the patients had positive anti-DNA and anti-CCP antibody, and the ANA was positive in 100%, with a predominantly homogeneous pattern. During the course of the disease, other clinical manifestations appeared in addition to the arthritis, which, together with the immunological profile, fulfilled the criteria for SLE (Tables I and II).

Of particular note, the anti-CCP was present in high titers in 80 percent of our patients, generally in titers of greater than 60 U. Anti-CCP antibodies have heretofore not been described in patients with SLE and erosive disease, whereby most reports of Rhupus to date have preceded the use of anti-CCP as a diagnostic and prognostic tool in RA (16, 19). This observation suggests to us the hypothesis that the presence of high titer anti-CCP antibodies in lupus predicts the development of erosive arthritis.

Anti-CCP associated SLE with erosive arthritis has been in a few other reports including Rothfield *et al.* (39) who recently described three female patients with a diagnosis of SLE and predominant articular manifestations, who had

cutaneous and hematologic disease and positive ANA of homogeneous pattern. Anti-DNA and low complement was present in two, and anti-Sm and anti-Ro were present in one patient. Rheumatoid factor was negative in all three patients, although of those that had more than ten years of disease with rheumatoid nodules, and deforming arthritis. Anti-CCP was present in two of three patients, but only one patient had evidence of erosions on radiographs. Other features in these patients included cutaneous vasculitis, alopecia, and class 4 glomerulonephritis.

Other reports of erosive arthritis in SLE include those of Cohen *et al.* (9), who reported on the coexistence of erosive arthritis in patients with SLE and the presence of the anti-RA33 antibody directed against the spliceosome constituents in patients with RA and SLE (9, 13, 15, 40). They concluded that the presence of anti-RA33 and rheumatoid factor was a marker of erosive articular disease in patients with SLE. Later, Mediwake *et al.* (14) reported similar findings in a retrospective study of 231 patients with SLE and deforming at with or without erosions. Only 10 patients (5%) had erosive disease. A recent report by Chan *et al.* (41) on patients with SLE and erosive arthritis (97 patients) concluded that patients who had a positive anti-CCP had a higher probability of developing erosive arthritis (odds ratio, 4.22, 95% CI 1.06, 16.87, $P < 0.05$), especially those with overt synovitis. They did not find a significant correlation between erosive arthritis and the presence of anti-CCP or HLA-DRB1*0401.

These cases emphasize the still blurred distinction between inflammatory rheumatic disease syndromes, as they are currently classified and understood. Features of these diseases are, as in these cases, overlapping, and even diagnostic tests with putatively high specificity such as the anti-CCP antibody do not fully serve to distinguish them. The patients presented in our series may be viewed as SLE with erosive arthritis, while at the same time it may be argued that they represent cases of RA with severe extraarticular manifestations. Serologic testing is of limited

value in making this distinction, as over 1/3 of patients with RA have measurable ANA titer, more common in patients with extraarticular involvement (42). However, malar rash, photosensitivity and glomerulonephritis, as noted in our patients, are not features of RA, while rheumatoid nodules, common in patients with erosive RA, were not detected in our patients (42).

The spectrum of disease and overlap between RA and SLE has been demonstrated in a population based cohort of patients with RA, in which 12.5% of patients with RA had at least four criteria and could be classified as having SLE according to ACR criteria (53) and were at higher risk for premature mortality (46, 47). Better understanding of the pathogenesis and disease mechanisms of RA and SLE will contribute to better diagnostic evaluation and treatment. These cases make it clear that high titers of anti-CCP may be detected in SLE and are a marker of deforming and erosive arthritis. Further studies will be needed to confirm and extend this hypothesis.

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