

Reproducible Tendinitis-Like Symptoms Related to Statin Therapy

To the Editor:

We present 2 cases of tendinitis-like symptoms that occurred during statin therapy. The symptoms of peritendon pain without involving the tendon itself resolved after the discontinuation of the statins. Then, the symptoms reoccurred after rechallenging with statin medication. This apparent class-related side effect occurred with 3 different statins. The tendinitis-like symptoms involved the Achilles, quadriceps, and deltoid peritendon area with normal creatine kinase levels. The resolution of symptoms occurred 2 to 8 weeks after statin discontinuation. These cases are followed by a review of the literature.

Case No. 1

A 43-year-old man with a medical history of hyperlipidemia, hypertriglyceridemia, and low high-density lipoproteins was started on 40 mg simvastatin therapy once a day. Eight weeks into the treatment, the patient noticed pain around the medial aspect of the left knee and foot near the quadriceps and Achilles tendons. His physical examination revealed tenderness around the Achilles and quadriceps tendons in the peritendon area. The simvastatin dose was decreased to 20 mg per day. Quadriceps tendinitis-like pain resolved after 4 weeks, but Achilles tendon pain increased in severity. When the patient took 40 mg simvastatin by mistake, his quadriceps tendinitis-like symptoms flared but resolved again after decreasing the dose to 20 mg per day. However, tendinitis-like symptoms of the Achilles tendon continued to increase in severity, which caused severe pain during skiing, forcing him to stop skiing.

Later, he experienced severe pain around his deltoid tendon. As a result of a progressive increase in pain, simvastatin was replaced with ezetimibe. After the discontinuation of simvastatin, his tendinitis-like symptoms gradually resolved in approximately 6 weeks and he went skiing again without any pain. He

was put on 2.5 mg rosuvastatin for persistent hypercholesterolemia. During 3 weeks of therapy, tendinitis-like pain in the Achilles and deltoid tendon regions flared again. His symptoms progressively increased interfering with his sleep. Rosuvastatin was stopped after 3 months and his symptoms completely resolved after 8 weeks. His initial low-density lipoprotein was 156 mg/dL, which decreased to 90 mg/dL while on 40 mg simvastatin daily and increased to 126 mg/dL on 10 mg ezetimibe alone. His triglyceride was in the 300 mg/dL range initially, which dropped to the 150 mg/dL range with additional of fish oil intake and the statin. His high-density lipoprotein was 35 mg/dL, which rose to approximately 40 mg/dL on simvastatin or rosuvastatin therapy. With a combination of rosuvastatin and ezetimibe, his low-density lipoprotein was decreased to 80 mg/dL along with increased in high-density lipoprotein to 40 mg/dL. His creatine kinase and liver function tests were always within the normal range. The patient is now asymptomatic on 10 mg ezetimibe 6 months after the discontinuation of rosuvastatin.

Case No. 2

A 70-year-old man with a history of hypercholesterolemia was started on 20 mg lovastatin and 300 mg gemfibrozil daily. After a few months of therapy, he experienced tenderness around his both Achilles tendons. His physical examination revealed tenderness around the Achilles tendons in the peritendon area sparing the actual tendons. His pain progressively increased interfering with his walking. Lovastatin was discontinued. After 2 weeks of being off lovastatin, his pain resolved. As a result of recurrent hyperlipidemia, his lovastatin was started at a lower dose of 10 mg and gemfibrozil was stopped. However, his tendinitis-like symptoms and pain flared again after 1 month of low-dose lovastatin therapy and resolved after 2 weeks off lovastatin. The patient remains asymptomatic without statin therapy. His creatine kinase and liver enzymes have been in the normal range during his treatment. Neither of the 2 patients has any musculoskeletal problems nor did they have any serologic studies available before or after their symptoms.

DISCUSSION

Rhabdomyolysis and musculoskeletal disorders such as myopathy are known side effects of statin therapy.¹⁻³ Rhabdomyolysis occurs at a very low frequency with the estimate of 2.3 per 10,000 person-years.^{4,5} The occurrence of tendinopathy is rarely reported. We present 2 cases of statin-induced pain in the peritendon area consistent with tendinitis-like symptoms. These symptoms resolved after statin discontinuation and recurred after rechallenging with different statins or lower dose. Symptoms occurred using 3 different statins suggesting a class-related side effect. Interestingly, the pain apparently involved tissue surrounding the tendons and not the tendons itself, and it was not associated with creatine kinase rise or abnormal liver enzymes.

The muscles near the tendons have the highest mechanical stress, which may explain the predisposition of the peritendon area. There is only one report about 4 patients with tendinopathy on statin therapy. Chazeraïn et al⁶ describes 3 men and one woman who were diagnosed with extensor tendosynovitis involving the hand in one, tibialis anterior in 2, and Achilles tendons in 2 cases. Two of the patients were on simvastatin and 2 on atorvastatin therapy. The tendinopathy similar to our cases developed 1 to 2 months after the treatment initiation and resolved within 1 or 2 months after discontinuation. In our cases, the pain was located in the peritendon area. However, no biopsy was performed to definitely determine the site of involvement. Fallip et al⁷ has reported 37 cases of statin-induced tendinopathies in a French population with a mean age of 58 years. Statin-induced tendinopathy was suspected in 27 cases; symptoms were delayed in onset with average of 11.4 months. Interestingly, Chazeraïn et al's report, similar to ours, shows Achilles tendinitis was the most frequent site of tendon involvement in 56.8% of cases with rupture of the tendon occurring in 16.2% of patients.

In a retrospective study of patients on statin therapy⁸ who were asked to report about any musculoskeletal symptoms, 165 of 815 (20%) experienced muscle symptoms attributed to lipid-lowering treatment. From this popula-

tion, almost half of the patients reported tendinitis-associated pain, which was the most common symptom second to cramp and stiffness. They found no correlation between symptoms and creatine kinase levels. All patients stated a clear chronologic link between their symptoms and their lipid-lowering treatment, either because they related the onset of symptoms to the initiation of therapy or because of an improvement after drug withdrawal. There were 2 peaks related to the onset of symptoms: the first one shortly after treatment within a few months in one fourth of the patients and the second after 12 months of the treatment. After restarting the lipid-lowering drugs, 63% of patients experienced recurrent pain. If we count only patients with recurrent pain after the second initiation of statin therapy, the incidence of tendinopathy will be approximately 13% in patients on statin therapy, which is much higher than the incidence of myopathy reported in the literature. Furthermore, up to 39% of patients with musculoskeletal pain used analgesics in this study suggesting that the pain has been severe enough in substantial numbers of patients. This study is very alarming and suggests that musculoskeletal symptoms are much more common in patients on statin and lipid-lowering treatments than reported in the literature. It is possible that high mechanical stress near the tendon area is responsible for this peculiar location of the symptoms.

Based on our and Franc et al's observations, we suspect that statin-induced tendinitis-like symptoms are more prevalent than what has been reported. The reason for this discrepancy in the literature is not known. In most statin and lipid-lowering trials, patients with muscle problems or those who were at risk for myopathy such as with liver or renal diseases were excluded.⁹ This selection bias, in part, could explain possible underreporting of these symptoms. Interestingly, large placebo-controlled trials have not described statin-induced tendinitis-like symptoms^{9–11} as a major adverse event. Therefore, a placebo-controlled trial with emphasis on statin-induced tendinitis-like pain is desirable. Magnetic resonance imaging or ultrasound could also be helpful to study future cases. Furthermore, it would be interesting to evaluate patients with statin-in-

duced tendinitis-like symptoms for the occurrence of x-ray abnormalities or abnormal serology for rheumatic disorders.

Mohammad-Reza Movahed, MD, PhD
S. Ahmad Samsamshariaat, MD

University of Arizona
Sarver Heart Center
Department of Medicine
Section of Cardiology
Tucson, Arizona
rmovahed@email.arizona.edu

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Anaphylactic Reaction in a Patient With Rheumatoid Arthritis: A Rare Side Effect of Methotrexate With Etanercept as a Provoking Factor?

To the Editor:

We report a case of an anaphylactic reaction after a methotrexate injection in a patient with rheumatoid arthritis. Of note in this case is the low dose of methotrexate used compared with earlier reports as well as the appearance of this adverse reaction after 8 years of methotrexate therapy and 40 weekly (subcutaneous) dosages of 25 mg methotrexate. It may be questioned whether the concomitant use of a tumor necrosis factor (TNF) and lymphotoxin-blocking agent (etanercept) had provoked this rare side effect in this patient.

A 46-year-old woman with rheumatoid factor-positive, erosive rheumatoid arthritis of 14 years' duration was treated with 5 mg prednisolone per day and 25 mg methotrexate g subcutaneously given weekly for 10 months. Previous therapy with sulfasalazopyridine as well as lower-dose (10 mg weekly) oral methotrexate in combination with cyclosporine was ineffective. Because remission had not been achieved with the aforementioned regimen, it was decided to add the TNF-blocking agent etanercept. She had no history of allergy; there were no allergic or atopic tendencies in her family.

She had received 6 months of etanercept therapy (25 mg subcutaneously given twice weekly) without any side effect. Ten minutes after the 41st methotrexate injection was given, she developed an urticarial rash without symptoms of breathlessness or hypotension. The rash subsided within 2 hours. A repeated etanercept injection 3 days later was well tolerated. Methotrexate injections given 1 and 2 weeks later in the outpatient department were followed by a pressure feeling on her chest. Physical examination revealed a macular rash and periorbital and general facial edema with-

out breathlessness. Her blood pressure fell 30 mm Hg. No respiratory wheezes could be heard. Methotrexate therapy was stopped. She recovered within 1 hour.

Supplemental laboratory investigations revealed normal values for total immunoglobulin E, methylhistamine, methylimidazol AA, and tryptase. Radioallergosorbent testing did not detect IgE antibodies directed to specific antigens. Antinuclear antibody testing was negative.

Four weeks later, intracutaneous testing with a 1:100 dilution of methotrexate revealed a positive response with a wheal of 15 mm. Control testing with 10 mg/mL histamine was positive (wheal 5 mm) and saline solution was negative (wheal 0 mm). Epicutaneous testing with methotrexate was performed in dilutions of saline 1:10, 1:100, and 1:100 and were all negative. The possibility that a contaminant provoked the allergic reaction was ruled out by performing the tests with syringes and saline solutions of the pharmacy batch that she used in the period of the clinical presentation of the allergic reaction on methotrexate. Analysis of the solutions for fungi, bacteria, and pyrogens was negative.

This is the first case of an anaphylactic reaction resulting from methotrexate in a patient with rheumatoid arthritis.

Several adverse cutaneous reactions to methotrexate have been reported; however, these are rare. Some papers have reported the development of leukocytoclastic vasculitis.^{1,2} Papular eruptions have been described in a few methotrexate (10–22.5 mg orally weekly) -treated patients with rheumatoid arthritis, but also in some patients with systemic lupus erythematosus and patients with mixed connective tissue disease. A fatal case of low-dose (25 mg intramuscular weekly) methotrexate-induced toxic epidermal necrolysis has been described in a patient with psoriasis.³

Anaphylactic reactions have been described after multiple and high doses of methotrexate, ranging from 50 mg/kg to 12 g/m² body surface area in patients receiving chemotherapy. These reactions included urticarial rash, tachycardia, agitation, hypotension, and breathlessness.^{4–6} There is one previous report on an anaphylactic reaction after treatment with methotrexate (75 mg once intramuscularly) for an ectopic pregnancy.⁷

Clinical data and positive skin test suggest an IgE-mediated hypersensitivity. Unfortunately, previous in vitro immunologic studies were unable to detect specific IgE in the patient's sera.⁸ Davis et al described a successful desensitization regimen to high-dose methotrexate after systemic anaphylaxis.⁹

In our case, the long duration of methotrexate treatment before the onset of this adverse effect is quite remarkable. In an earlier report, Goldberg¹⁰ suggested that bacillus Calmette-Guerin used as adjuvant therapy in human cancer might potentiate the development of an immune reaction to methotrexate. Combined therapy with methotrexate and 2 other drugs had been described as provoking side effects, either cutaneous or generalized, resulting from drug-drug interactions or unidentified mechanisms. High-dose methotrexate combined with trimethoprim-sulfamethoxazole provoked toxic epidermal necrolysis in a boy treated for leukemia¹¹; an acute febrile toxic reaction had been reported in 4 patients with rheumatoid arthritis receiving combined therapy with methotrexate and azathioprine.¹²

We hypothesize that the concomitant use of etanercept had provoked an allergic reaction in our methotrexate-treated patient. T_H1 cytokines such as TNF- α , present in active rheumatoid arthritis, inhibit the generation of a T_H2-driven immune response, predominantly present in allergic diseases.¹³ The suppression of the T_H1 cytokines by a TNF-blocking agent allows the T_H2-activated pathway to express itself clinically as an anaphylactic reaction or asthma. Asthma has also been reported as a rare adverse event in patients treated with TNF-blocking agents.¹⁴

Although the occurrence of allergic diseases is sporadic, we recommend awareness of reactions beyond the skin in TNF blocker-treated patients.

Pieterella M. Houtman, MD, PhD

Tim L. Jansen, MD, PhD

Department of Rheumatology
Medical Centre Leeuwarden
Leeuwarden, The Netherlands

Rob Blanken, MD

Department of Dermatology
Medical Centre Leeuwarden
Leeuwarden, The Netherlands

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Thyroid Status in Patients With Systemic Sclerosis

To the Editor:

Systemic sclerosis (SSc) is an autoimmune disorder of the connective tissue characterized by widespread vascular lesions and fibrosis of the skin and

internal organs. Identification and characterization of autoantibodies in SSc is pivotal, because they provide useful information to define clinical subset and progression. It has been hypothesized that patients with SSc may develop hypothyroidism¹⁻⁴ and thyroid autoantibodies.^{5,6} To further evaluate this topic, we measured free thyroxine (FT4), thyroid-stimulating hormone (TSH), the natural logarithm of TSH against FT4 (lnTSH/FT4), antithyroglobulin (TGAb), and antithyroperoxidase (TPOAb) antibodies in 38 consecutive female patients with SSc (mean age, 49.3 years; mean disease duration, 8 years; 20 with limited and 18 with diffuse disease patterns) who fulfilled the American Rheumatism Association's criteria for the diagnosis of SSc.⁷ Thirty females control subjects, matched for age and for environmental habits, were recruited among healthy hospital personnel. Eighteen patients with SSc were currently under cyclic iloprost infusions. No patient with SSc or healthy control was currently taking medications known to influence thyroid function, including aspirin, antihypertensive or lipid-lowering drugs, hormonal therapies, and nonsteroidal antiinflammatory agents nor displayed clinical signs or symptoms of overt thyroid disease. All subjects gave informed consent for being tested. Blood samples were collected in the morning after an overnight fast in vacuum tubes containing no additives (Becton-Dickinson, Oxford, U.K.). After centrifugation at 1500 g for 10 minutes at room temperature, serum was separated, stored in aliquots, and kept frozen at -70°C until measurement. FT4 and TSH were measured by a 2-site chemiluminescent immunometric assay on Immulite 2000 (DPC, Los Angeles, CA). TGAb and TPOAb were evaluated by enzyme-labeled, chemiluminescent sequential immunoassay on Immulite 2000 (DPC). According to the manufacturer's specification, total coefficients of variation comprised between 5% and 10%. Results of FT4 and TSH measurements and value distributions of TGAb and TPOAb were analyzed by unpaired Student *t* test and χ^2 test, respectively. The level of statistical significance was set at $P < 0.05$.

Despite a heterogeneous distribution, patients with SSc showed a signifi-

TABLE 1. Results of Free Thyroxine (FT4), Thyroid-Stimulating Hormone (TSH), the Natural Logarithm of TSH Against FT4 (lnTSH/FT4), Antithyroglobulin (TGAb), and Anti thyroperoxidase (TPOAb) Antibody Measurements in Patients With Systemic Sclerosis (SSc) and Healthy Matched Controls*

	Healthy Controls	SSc Patients	<i>P</i>
N	30	38	
FT4 (ng/L)	13.2 ± 1.4	12.2 ± 2.0	0.024
TSH (mU/L)	1.32 ± 0.78	2.06 ± 1.36	0.017
lnTSH/FT4	0.010 ± 0.048	0.046 ± 0.059	0.011
TPOAb >35 U/mL	3/30 (10%)	7/38 (18%)	0.005
TGAb >40 U/mL	3/30 (10%)	3/38 (8%)	0.483

*FT4, TSH, and lnTSH/FT4 values are given as mean $\pm$ standard deviation.

cantly lower FT4 and increased TSH and lnTSH/FT4 values (Table 1). After excluding subjects with thyroid autoantibodies exceeding the diagnostic thresholds for adults (8 patients with SSc: 2 with both TPOAb and TGAb, 5 with TPOAb, and one with TGAb; 4 healthy controls: 2 with both TPOAb and TGAb, one with TPOAb, and one with TGAb), this trend remained substantially unchanged. In particular, patients with SSc still displayed lower values for FT4 (12.1 ± 2.0 vs 13.3 ± 1.3 ng/L, $P = 0.021$) and increased lnTSH/FT4 (0.032 ± 0.010 vs 0.010 ± 0.037 , $P = 0.043$) and TSH values (1.66 ± 0.97 vs 1.27 ± 0.52 mU/L, $P = 0.040$). The percentage of patients displaying values exceeding the reference range was significantly different between patients with SSc and healthy controls for TPOAb, but not for TGAb (Table 1). Patients with SSc with thyroid autoantibodies exceeding the respective diagnostic thresholds displayed significantly increased lnTSH/FT4 (0.100 ± 0.052 vs 0.032 ± 0.052 , $P = 0.001$) and TSH (3.53 ± 1.62 vs 1.66 ± 0.97 mU/L, $P < 0.001$), but not significantly different FT4 (12.4 ± 1.9 vs 12.1 ± 2.0 ng/L, $P = 0.338$) than those with normal TPOAb and/or TGAb.

Patients with SSc may develop a heterogeneous pattern of autoantibodies associated with a variety of clinical manifestations. Besides traditional anti-Scl-70 and antinucleolar antibodies, the association of SSc with less specific autoantibodies such as TGAb and TPOAb is as yet inconclusive, limiting the clinical use of their evaluation in this subset of patients.^{1,8} It was earlier reported that a substantial proportion of patients with

SSc, up to 55%, might develop antibodies to thyroid antigens, especially against microsomal thyroid peroxidase (TPO), without exhibiting overt thyroid dysfunction.^{1,5,6} In agreement with these observations, we confirm a significantly increased prevalence of TPOAb in patients with SSc. However, we provide evidence that these patients display a trend toward a silent autoimmune hypothyroidism, as demonstrated by increased lnTSH/FT4 values, which appears more evident in patients with increased thyroid autoantibodies and which was not evaluated in previous investigations. Earlier studies demonstrated that the level of this innovative marker of thyroid function provides further information to identify patients with primary alterations of thyroid hormone secretion and its value is usually lower in patients with established thyroid hormone resistance.⁹ Taken together, these data indicate that antithyroid antibodies might be responsible for the appearance of some hypothyroidism in SSc, and monitoring of thyroid function might be advisable in patients affected by this peculiar autoimmune disorder.

Giuseppe Lippi, MD

Istituto di Chimica e Microscopia Clinica
Dipartimento di Scienze Morfologico-Biomediche
Università degli Studi di Verona
Verona, Italy

Paola Caramaschi, MD

Dipartimento di Medicina Clinica
Sezione di Medicina Interna B
Università degli Studi di Verona
Verona, Italy

Martina Montagnana

Gian Luca Salvagno, MD

Istituto di Chimica e Microscopia Clinica
Dipartimento di Scienze Morfologico-Biomediche
Università degli Studi di Verona
Verona, Italy

Alessandro Volpe, MD

Dipartimento di Medicina Clinica
Sezione di Medicina Interna B
Università degli Studi di Verona
Verona, Italy

Gian Cesare Guidi, MD

Istituto di Chimica e Microscopia Clinica
Dipartimento di Scienze Morfologico-Biomediche
Università degli Studi di Verona
Verona, Italy

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Anticardiolipin Antibodies in Scleroderma

To the Editor:

Anticardiolipin antibodies (aCLs) have been associated with arterial and venous thrombosis, pulmonary hypertension, and chronic leg ulcers.¹ Arterial vasculopathy has also been reported in association with antiphospholipid antibodies.² Systemic sclerosis (SSc) is characterized by proliferative and obliterative vascular lesions.³ Pulmonary hypertension is a well-described complication of limited systemic sclerosis (lcSSc).⁴

Studies of aCLs in SSc have yielded conflicting results.^{5–16} We investigated sera from 82 patients with SSc for the presence of IgG and IgM aCLs and sought correlation with other clinical and laboratory features of SSc.

Eighty-two patients with SSc were investigated (71 women and 11 men). All patients fulfilled the criteria for the classification of SSc.¹⁷ Twenty-five patients had lcSSc, 49 patients had diffuse systemic sclerosis (dcSSc), and 8 had an overlap syndrome of scleroderma and another rheumatic disease. One hundred healthy unselected controls as well as 100 healthy selected control patients were tested. Healthy control patients were selected by the absence of any clinical manifestations related to the aCL syndrome, medication, pregnancy, or recent infection.

IgG and IgM aCLs were detected by using BIOPOSTAR READS enzyme-linked immunosorbent assay. Each sample was assayed in triplicate. Results of patient samples were expressed in anticardiolipin units calculated against IgG and IgM cardiolipin standards donated by Dr. E. N. Harris. Values greater than 2 standard deviations (SDs) above the mean of 100 unselected control sera were considered elevated (22.6 GPL for IgG aCL and 10.8 MPL for IgM aCL). Results were analyzed by the χ^2 test with Bonferroni correction.

The opinions or assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

Ten of 82 patients (12.2%) had an elevated IgG aCL (mean, 36.5 GPL) and 3 of 82 patients (3.7%) had an elevated IgM aCL (mean, 14.9 MPL). There was no difference in aCL positivity between disease subsets. Mean values of the IgG and IgM aCL-negative patients were 11.2 GPL and 3.9 MPL, respectively. Mean IgG and IgM aCL for unselected controls were 12 GPL and 5 MPL, respectively. Two unselected normal control patients had a positive IgG aCL, whereas none of the selected controls were positive. The majority of the aCL-positive sera was of low titer with only 4 of 10 greater than 5 SDs above the mean and only one of 10 greater than 7 SDs above the mean. Four positive IgG aCL patients had serial testing with 3 of 4 losing their positive aCL over a 7-year period. Four negative aCL patients had serial testing with aCL levels remaining negative over a period of 1 to 6 years.

The 3 positive IgM aCL patients included a patient with lcSSc, a patient with dcSSc, and a patient with linear scleroderma. The patient with linear scleroderma also had an elevated IgG aCL.

The serologic and clinical features of the 10 aCL-positive patients are listed in Table 1. IgG aCL values ranged from 23.6 to 61.6 GPL. Only one patient (no. 9) had both an elevated IgG and IgM aCL. The anticentromere antibody (ACA) pattern was seen in 2 of 3 aCL-positive patients with lcSSc, whereas the scleroderma antibody (SCL-70) was seen in 3 of 6 aCL-positive patients with dcSSc.

A variety of clinical and laboratory variable associated with SSc or the antiphospholipid syndrome were analyzed for statistical significance. No significant correlations were found between the presence of aCLs and the following clinical features: deep venous thrombosis, pulmonary embolus, livedo reticularis, cutaneous or systemic vasculitis, thrombocytopenia, cerebral vascular disease, spontaneous abortions, Raynaud phenomenon, peripheral neuropathy, diarrhea, renal failure, hypertension, pulmonary hypertension, arthritis, cough, or pleural disease. No significant correlation was found between the presence of aCLs and the following laboratory variables: decreased

renal function (creatinine >1.3 mg/dL), proteinuria, antinuclear antibodies, SCL-70, ACA, dsDNA antibody, thrombocytopenia, anemia, or abnormal liver associated enzymes.

Studies of aCLs in patients with SSc have reported conflicting results.⁵⁻¹⁶ (Table 2) Positive IgG aCLs have been reported in 0% to 22% in patients with SSc with IgM aCL found in 3% to 8.6%.⁵⁻⁷ Overall, aCL positivity (IgG and IgM) in SSc has been reported from 5% to 25%.^{8,12,14,18} Variation of aCL positivity between studies may result from where each author establishes aCL

positivity (2, 3, 7, or 10 SDs above the mean). Anticardiolipin antibodies have also been reported positive in over 50% of healthy elderly patients,¹⁸ which would increase overall aCL positivity of elderly patients with SSc.

Our study shows no association with aCLs and any clinical manifestation of scleroderma. Picallo's series also reported a negative association of aCL and the presence of restrictive lung disease and increased disease score.¹³ An increased incidence of pulmonary hypertension has been reported in scleroderma patients positive for beta 2-glyco-

protein I.^{12,15} Other studies have shown no correlation of any aCL titer or isotype with clinical or laboratory manifestations of SSc.^{5,6,10} A recent study reported an association of antiphosphatidylserine-prothrombin complex antibodies with thromboembolism, peripheral ischemia, and lung involvement in some patients with SSc.¹⁶

Our study also confirms previous reports that aCL antibodies found in SSc are usually of low titer^{5,6} and low prevalence.¹⁵ The decline of aCL antibody titer positivity seen in 3 of 4 of our patients was previously noted in one patient reported by Seibold⁵ who had a high titer of IgA aCL associated with recurrent first-trimester spontaneous abortions, which decreased after her second fetal loss. Our series noted an equal number of positive aCLs in patients with lcSSc and dcSSc. Picallo has reported an increased incidence of positive aCLs in patients with lcSSc.¹³

In conclusion, aCLs may be seen in a small percentage (12.2%) of patients with SSc but are of no clinical significance. Anticardiolipin antibodies were not associated with clinical or laboratory findings in SSc. Routine testing for aCLs in patients with SSc is not warranted unless selected patients have clear evidence of the antiphospholipid antibody syndrome.

TABLE 1. aCL-Positive Patients: Serologic and Clinical Features

Patient No.	aCL		ANA	SCL-70/ Centromere		SSc Subset
	IgG	IgM				
1	46.4	2.3	neg-	—	—	lcSSc
2	35.0	2.3	1:640 sp	—	+	lcSSc
3	23.6	6.3	1:240 fs	+	—	dcSSc
4	61.6	3.0	1:320 h/sp	+	—	UCTD
5	34.7	9.2	1:160 sp	+	—	dcSSc
6	41.4	9.2	neg	+	—	dcSSc
7	25.3	9.2	1:16 sp-	—	—	dcSSc
8	27.3	9.2	1:256 sp/nuc	—	+	lcSSc
9	38.7	14.6	1:256 sp/nuc	—	+	lcSSc
10	30.7	4.6	1:640 nuc	—	—	dcSSc/RA

aCL indicates anticardiolipin antibody; ANA, antinuclear antibody; neg, negative; fs, fine speckled; sp, speckled; nuc, nucleolar; ND, not done; lcSSc, limited systemic sclerosis; dcSSc, diffuse systemic sclerosis; UCTD, undifferentiated connective tissue disease; RA, rheumatoid arthritis.

TABLE 2. Anticardiolipin Antibodies in SSc

Reference	No. of Patients	Method	IgG aCL	IgM aCL	IgA aCL	Associations
5	35	ELISA	0%	8.6%	23%	No association with clinical subsets or disease manifestations
6	37	RIA	22%	3%	ND	All aCL-positive patients with dcSSc (not statically significant)
7	23	ELISA	11.2%	ND	ND	No association with increased thrombosis or thrombocytopenia
8	28	ELISA	25%	(IgG	and IgM)	5 of 7 positive aCL patients with "severe" SSc
9	63	ELISA	4.8%	aCL		aCL in SSc rarely manifest clinically; no difference in prevalence lcSSc or dcSSc
13	105	ELISA	25.5%	(IgG)	(IgM, IgA)	+aCL associated with "widespread skin and visceral involvement
14	103	ELISA	25.2%	(IgG)	(IgM, IgA)	Significant association between +aCL and myocardial ischemia or necrosis; no patients with antiphospholipid syndrome
17	40	ELISA	5% (IgG)	(IgM)	ND	No association in SSc; higher incidence of ANA positivity as well as antibodies to SSA and RNP were found in aCL-positive patients
19	35	ELISA	"small numbers"			Raynaud phenomenon in 66% of patients with SLE with high titer aCL (>10 SD above norm); one of 3 patients with SSc with high aCL had digital artery thrombosis before development of skin disease

SSc indicates systemic sclerosis; aCL, anticardiolipin antibody; ELISA, enzyme-linked immunosorbent assay; ND, not done; dcSSc, diffuse systemic sclerosis; lcSSc, limited systemic sclerosis; RNP, ribonucleoprotein; SLE, systemic lupus erythematosus.

Raymond J. Enzenauer, MD

Rheumatology Services
Fitzsimons Army Medical Center (FAMC)
Aurora, Colorado

David H. Collier, MD

University of Colorado Health Sciences
Center
Denver, Colorado

Luis R. Lopez, MD

Biostar Medical Products
Boulder, Colorado

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Concomitant Onset of Graves Disease and Rheumatoid Arthritis After a Serious Life Event

To the Editor:

A 65-year-old woman was referred with a 3-week history of headaches, arthralgias of the hips and shoulders, weakness, weight loss of 3 kg, and eye discomfort. She had no history of tobacco or alcohol use. She had not been feeling well for the last 6 months after the sudden death of her husband.

Medical history was significant for hypertension treated with 10 mg amlodipine per day for the last year. Her only sister was on therapy for hyperthyroidism resulting from Graves disease.

Clinical examination revealed symmetric synovitis of the wrists, ankles, carpometacarpal and metatarsophalangeal joints. She also had exophthalmos, periorbital edema, tremor, and pretibial myxedema. She had no clinical or radiographic signs of thyroid acropachy.

The laboratory examination revealed anemia (hematocrit = 33%), high erythrocyte sedimentation rate (ESR; 75 mm/h) and C-reactive protein (CRP; 3.5 mg/dL; normal values, 0.08–0.8 mg/dL). Thyroid-stimulating hormone (TSH) was depressed (0.09 μ IU/mL, normal values, 0.3–4 μ IU/mL), free thyroxine-3 (FT3)

was 6.81 pg/mL (normal values, 2.2–4.7 pg/mL), and FT4 was 3.26 ng/dL (normal values, 0.8–2 ng/dL). Antinuclear, antineutrophil–cytoplasmic, anti-Ro/SSA, anti-La/SSB antibodies, and rheumatoid factor were negative. The diagnosis of Graves disease was established based on findings of ultrasonography and iodine scan of the thyroid gland, computed tomography of the orbits (proptosis and thickening of the periorbital muscles), and clinical signs of hyperthyroidism. Therapy with 30 mg methimazole per day was initiated and during the next month, symptoms of hyperthyroidism were improved and TSH returned to normal. Polyarthritides and anemia and high values of ESR and CRP persisted.

Possible articular manifestations of thyroid disease were excluded and a concomitant diagnosis of seronegative rheumatoid arthritis (RA) was made according to the American College of Rheumatology criteria (4 of 7). The patient received methotrexate (15 mg/wk) and on the second reevaluation, 1 month later, indices of systemic inflammation were ameliorated with values of hematocrit of 39% and ESR of 22 mm/h, whereas arthritis was improved with no other exacerbation of arthritis over the next 6 months.

In cases of inflammatory arthritis in a hyperthyroid patient with Graves disease, the clinician has to look for possible rheumatic manifestations of Graves disease: scapulohumeral periartthritis,¹ drug-induced arthritis,² fibromyalgia,³ thyroid acropachy,⁴ gout,⁵ and also for the possible coexistence of another autoimmune disease.

Rheumatoid arthritis and Graves disease are 2 common autoimmune diseases with similar prevalence in the general population.^{6,7} Both of them affect predominantly middle-aged women. However, there is no direct evidence to support clear causality implicating common genetic or environmental factors. Recently, Prichard et al reported a possible common pathogenetic mechanism in Graves disease and RA involving insulin-like growth factor receptor-1 (IGF1-R) on fibroblasts, a pathway that mediates inflammatory responses.⁸ From a genetic point of view, Kochi et al suggested that there is a functional variant in FCRL3

gene that is associated with RA and several autoimmune diseases, including Graves disease.⁹

Epidemiologically, Matos-Santos et al suggest that serious life events are precipitating factors for the onset of Graves disease,¹⁰ whereas it is known that stress affects the immune system either directly or indirectly through the neuroendocrine system.¹¹ For patients with RA, the role of stress as a disease-permissive factor seems to be equivocal.¹²

Taken together, although indirectly, these data indicate that Graves disease and RA share possible common genetic, pathophysiological, and environmental features.

The concomitant onset of Graves disease and RA in our patient is of interest. Of note, the symptoms of Graves disease and RA followed the sudden death of her husband. The coincidence of Graves disease in her only sister supported a genetic predisposition to autoimmunity. Practically, it is very difficult but challenging to prove that stress was the main triggering factor for the onset of Graves disease and RA. The temporal relationship suggests a potential linkage.

Leonidas A. Bourikas, MD
Prodromos I. Sidiropoulos, MD

Division of Rheumatology, Clinical
Immunology and Allergy
University of Crete
University Hospital
Heraklion, Greece

Georgios N. Goulielmos, PhD

Division of Internal Medicine
University of Crete
University Hospital
Heraklion, Greece

Dimitrios T. Boumpas, MD, FACP

Division of Rheumatology, Clinical
Immunology and Allergy
Division of Internal Medicine
University of Crete
University Hospital
Heraklion, Greece

Heraklis D. Kritikos, MD

Division of Rheumatology, Clinical
Immunology and Allergy
University of Crete
University Hospital
Heraklion, Greece

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