Drug-Induced, Ro/SSA-Positive Cutaneous Lupus Erythematosus

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Objective: To study the clinical and immunopathologic findings of drug-induced, Ro/SSA-positive cutaneous lupus erythematosus (CLE).

Design: Retrospective medical and laboratory record review.

Setting: Immunodermatology Division of Johns Hopkins Hospital (Baltimore, Md).

Patients: Of 120 patients found to have anti-Ro/SSA antibodies by hemagglutination and/or double immunodiffusion, 70 had clinical and immunopathologic confirmation of CLE. Fifteen of these 70 patients had a history of new drug exposure, defined as less than 6 months, associated with disease development.

Results: The disease-associated drugs included hydrochlorothiazide (5 patients), angiotensin-converting enzyme inhibitors (3 patients), calcium channel blockers (3 patients), interferons (2 patients), and statins (2 patients). The most common presentations were photodistributed diffuse erythema and subacute CLE-type lesions without evidence of significant systemic disease. All specimens revealed interface dermatitis and fine granular IgG deposition along the basement membrane zone and throughout the epidermis. Most patients experienced improvement or resolution of clinical lesions within 8 weeks and decrease of Ro/SSA titers within 8 months after discontinuation of drug treatment.

Conclusions: Antihypertensive drugs are the most commonly associated with Ro-positive CLE. Clinical and immunopathologic features of this drug-induced variant do not seem to differ from the idiopathic disease. In most cases, the disease improves or resolves on discontinuation of the offending drug treatment. It is not known if these drugs precipitate disease in patients who have subclinical disease. Drug-induced Ro/SSA-positive CLE should be included on the differential diagnosis in patients presenting with photosensitive or subacute CLE-type eruptions.

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SUBSETS OF cutaneous lupus erythematosus (CLE) associated with the presence of anti-Ro/SSA antibodies include the following1-9: (1) drug-induced lupus erythematosus (LE); (2) neonatal LE; (3) LE with inherited C2 and C4 deformities; (4) LE in the elderly; (5) Sjögren syndrome; (6) LE and benign hypergammaglobulinemic purpura of Waldenstrom syndrome (lymphocytic vasculitis); (7) LE and photosensitivity; (8) subacute CLE (SCLE); and (9) LE with erythema multiformelike lesions (Rowell syndrome). The most recent and least characterized subset of LE has been the phenomenon of drug-induced Ro/SSA-positive CLE.10 Patients typically exhibit a photosensitive eruption with SCLE features. In contrast to the classic antihistone drug–induced LE (induced by, for example, procainamide or hydralazine), drug-induced Ro/SSA-positive CLE is virtually always associated with cutaneous disease and a wider spectrum of drugs. For the present report, we observed patients with clinical and immunopathologic confirmation of Ro/SSA-positive CLE and examined the subset of patients with drug-induced or -exacerbated disease.

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Our index case involved a 58-year-old white man with hypercholesterolemia and hypertension presenting with a new skin eruption. He had been undergoing atenolol therapy for 6 years and had recently had 40 mg of daily pravastatin added to his regimen. During the initial week of pravastatin therapy he started experiencing generalized and progressive myalgias exacerbated by exercise. He denied...
muscle weakness, dysphagia, dyspnea, or Raynaud phenomenon.

Six weeks after starting pravastatin treatment, he developed an asymptomatic cutaneous eruption. Clinical and laboratory evaluations were performed at that time, with the following results: creatine kinase, 220 U/L (normal, 24-170 U/L); alanine aminotransferase, 48 U/L (normal, 0-31 U/L); aspartate aminotransferase, 47 U/L (normal, 0-31 U/L); lactate dehydrogenase, 300 U/L (normal, 122-200 U/L); and aldolase, 8 U/L (normal, 1-3.5 U/L). A diagnosis of possible statin-induced dermatomyositis was made.

Subsequent muscle biopsy specimen analysis, electromyogram, and magnetic resonance imaging showed no evidence of an inflammatory myopathy. He was treated with 40 mg/d of prednisone, and his pravastatin regimen was reduced to 20 mg/d. Four weeks later, partial improvement of the muscular and cutaneous disease was observed, but there were no changes in the levels of muscle enzymes (creatine kinase).

Physical examination revealed a photodistributed erythema and annular, scaly, SCLE-type lesions on the trunk and proximal extremities (Figure, A). Examination findings were negative for periangual telangiectasias, Gottron papules, peri-orbital heliotrope eruption, psoriasiform scaly dermatitis, and centripetal flagellate erythema. Proximal muscle strength bilaterally was 5/5. Serologic study findings from hemagglutination and double immunodiffusion were positive for Ro/SSA and negative for La/SSB, nRNP, Sm, antihistone, and Jo-1 antibodies.

Pravastatin treatment was discontinued, and sunscreen with sun protection factor 45 and avobezone were prescribed. Two weeks later, all of the muscular symptoms had resolved. Approximately 8 weeks later, the skin lesions had improved, and creatine kinase concentration was within normal limits. Results of Ro/SSA serologic hemagglutination studies were weakly positive, and double immunodiffusion results were negative at 8 months' follow-up.

METHODS

A retrospective medical and laboratory record review was performed for patients who underwent serologic evaluation for anti-Ro/SSA antibodies by hemagglutination and/or double immunodiffusion during a 10-year period from July 1991 to March 2002 at the Division of Immunodermatology at the Johns Hopkins Hospital. We determined which patients had clinical and immunopathologic evidence of CLE and anti-Ro/SSA antibodies and evaluated their medical records for possible association between recent drug exposure and triggering or exacerbation of the Ro/SSA-positive CLE.

PROCEDURE FOR DOUBLE IMMUNODIFFUSION ANTIBODY TEST FOR PRECIPITINS

Ro/SSA, nRNP, Sm, La/SSB, and Jo-1 antibodies were detected using standard protocol for the double immunodiffusion antibody test for precipitins. Rabbit thymus extract (Zeus Scientific Inc, Raritan, NJ) was used for nRNP, Sm, and La/SSB antibody detection, and bovine spleen extract (Zeus Scientific Inc) was used for Ro/SSA antibody detection.
**Hemagglutination Assay for Ro/SSA Detection**

The Hemagen ENA (extractable nuclear antigens) series (Hemagen Diagnostics, Columbia, Md) was used according to protocol to detect Ro/SSA antibodies via red cell agglutination.12,14 A reaction was deemed positive if agglutination of cells by antibodies present in the patient or control serum resulted in the formation of a smooth mat covering the bottom of the well. If the red cells settled to the bottom of the well in a compact button in the clear medium, the reaction was deemed negative.

**Direct Immunofluorescence Histologic Evaluation**

Histologic staining with hematoxylin-eosin and direct immunofluorescence were completed according to standard protocol.15,16 In short, for direct immunofluorescence examination, frozen sections of lesional skin specimens were incubated with antibodies fluorescein labeled to human IgG, IgM, IGA, C3, and fibrinogen, and the specimens were examined using a fluorescence microscope. For routine histologic examination, formalin-fixed and paraffin-embedded 4-mm skin biopsy specimens were sectioned and stained with hematoxylin-eosin, and the specimens were examined using a light microscope.

**Results**

We found 120 patients who had positive serologic hemagglutination and double immunodiffusion findings for anti-Ro/SSA antibodies. Of these, 70 had definitive clinical evidence of CLE with immunopathologic confirmation. We found 15 patients who had an association between a new drug exposure (drugs initiated less than 6 months prior to disease onset) and development of the disease (Table 1).

The most common clinical manifestation in our patients was a photodistributed erythema. The second most common manifestation was the typical scaly, annular plaques of SCLE (Figure). The mean time to development of clinical disease after initiation of treatment with the drug was 7.27 weeks (range, 4-20 weeks). The main therapeutic intervention was discontinuation of treatment with the offending agent, although some patients required topical corticosteroid and/or hydroxychloroquine therapy because their disease was originally misdiagnosed as idiopathic CLE. Most patients experienced clinical improvement 6 to 12 weeks after discontinuation of treatment with the associated drug (mean recovery time, 7.8 weeks) (Table 1).

All patients exhibited anti-Ro/SSA and antinuclear antibodies in a fine speckled pattern, with titers ranging from 1:160 to 1:1380. Additionally, 7 patients developed anti-La/SSB antibodies. Findings for anti-Sm, anti-RNP, anti-dsDNA, and antihistone antibodies were negative in all patients. Four patients exhibited elevated erythrocyte sedimentation rates. The 2 patients undergoing treatment with statin drugs tested negative for Jo-1 antibodies and elevated creatine kinase levels. All patients had normal values of C3, C4, complete blood counts, and urinalyses (Table 1).

Initial Ro/SSA serologic findings were positive in all patients for hemagglutination and positive in 10 (67%) of 15 patients with double immunodiffusion (precipitins). At 8 months’ follow-up, 9 (60%) of 15 patients tested positive or weakly positive for anti-Ro/SSA antibodies via hemagglutination. Only 3 (20%) of 15 patients tested positive for antibodies under double immunodiffusion (Table 1).

All patients’ skin immunopathologic findings demonstrated interface dermatitis with perivascular lymphocytic infiltrates, scant mucin, and perivascular infiltrates. Direct immunofluorescence revealed dustlike granular IgG along the basement membrane zone and
lower epidermis in all specimens and scant granular C3 deposition in only 6 of the specimens.

**COMMENT**

Classic drug-induced LE is characterized by systemic disease with a lower incidence of nephritis, lack of cutaneous involvement, and the presence of antihistone antibodies. A limited number of drugs have been associated with this phenomenon, including procainamide, hydralazine, isoniazid, and minocycline.17,18

More recently, however, a new subset of drug-induced LE characterized primarily by cutaneous disease and the usual presence of anti-Ro/SSA antibodies has been described.9,10 The most common drugs associated with this disease are antihypertensive drugs, including hydrochlorothiazide, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, and systemic antifungal agents, including griseofulvin and terbinafine. Other drugs have been reported as well (Table 2).19-39 Interestingly, there have been reports of oxprenolol- and procainamide-induced SCLE37,39; unfortunately, Ro/SSA serologic test results were not available in these cases. In patients with clinical features of SCLE and immunopathologically proven LE who have been recently exposed to an implicated drug, drug-induced CLE must be considered, despite the absence of Ro/SSA antibodies. Even with idiopathic SCLE, Ro/SSA antibodies are present in only about 75% of cases.3

In the present study, we have studied the records of patients who had positive Ro/SSA serologic findings, clinical and immunopathologic evidence of CLE, and an association between the development of disease and new drug exposure of less than 6 months. We confirmed that antihypertensive drugs including hydrochlorothiazide, calcium channel blockers, and ACE inhibitors are the most common drugs implicated in drug-induced Ro/SSA-positive CLE. Although interferon alfa has been known to induce systemic LE and antinuclear antibody produc-

<table>
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<tr>
<th>Drug</th>
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<tbody>
<tr>
<td>Hydrochlorothiazide</td>
<td>9, 19</td>
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<tr>
<td>Hydrochlorothiazide/triamterene</td>
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<td>Chlorothiazide</td>
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<td>Cilazapril</td>
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<td>Interferon beta</td>
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<td>Terbinafine</td>
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This is the first report to describe its association with Ro/SSA-positive CLE. Interferon beta–induced Ro/SSA-positive CLE, however, has been reported.23 Although there has been a reported case of glyburide-induced Ro/SSA-positive CLE, we attributed the disease of our patient to enalapril exposure because ACE inhibitors are better known to induce this disease and termination of enalapril treatment resulted in clinical resolution.

Most of the offending agents recognized in the present analysis triggered disease 4 to 8 weeks after the new drug exposure. Patient 15, however, being treated with interferon beta, did not develop disease until 20 weeks of drug exposure. Thus, it is possible that this agent is more likely to cause “late-onset” skin disease than the “early-onset” disease seen with the other drugs. It is important to note that we did not find a significantly greater or lesser frequency of cases of Ro/SSA-positive CLE induced by known implicated agents than did previous studies. Additionally, since our study included patients evaluated between 1991 and 2002, it is possible that newer drugs that may be implicated in this disease have been overlooked or underreported in the present study.

There have been a few isolated reports of statin-induced dermatomyositis.40-42 However, the present study illustrates that myopathy induced by statin use, a very common feature of this drug class, can be associated with elevated muscle enzymes with no other specific findings (eg, Gottron papules, periorbital heliotrope eruption, psoriasiform scalp dermatitis, or centripetal flagellate erythema) or sensitive findings (eg, periungual telangiectasias or pock-loderma of the trunk) of dermatomyositis. Photosensitivity can be seen in dermatomyositis but virtually always in association with the specific above-mentioned features of the disease. Evolution of myopathy in our index case was consistent with a toxic drug effect secondary to pravastatin treatment. Muscle biopsy specimen analysis, imaging studies, and functional studies revealed no evidence of inflammatory myopathy.

Although dustlike IgG deposition in the basement membrane zone is not pathognomonic, it did favor a diagnosis of Ro/SSA-positive CLE in our patient. Furthermore, the presence of annular scaly plaques (SCLE-type lesions) and anti-Ro/SSA antibodies in dermatomyositis is extremely unusual, again favoring a diagnosis of Ro/SSA-positive CLE. Thus, it is imperative to have good clinical and immunopathologic and serologic correlations in these cases. To our knowledge, this is the first report of statin-induced Ro/SSA-positive CLE.

Interestingly, we did not have any patients with Ro/SSA-positive CLE induced by systemic antifungal agents. However, this is likely owing to sampling error because the association of these drugs has been well reported in the literature.

Our study found that the most common clinical manifestation of drug-induced Ro/SSA-positive CLE in our patients was a photosensitive erythema. The second most common manifestation was the typical scaly annular plaques of SCLE described by Sontheimer et al.3,5 Immunopathologic examination of all our patients, regardless of the clinical presentation, revealed an interface dermatitis with fine, dustlike granular IgG deposition along the basement membrane zone and throughout...
the lower epidermis. The mean time to development of disease after initiation of treatment with an implicated drug was 7.27 weeks (range, 4-20 weeks). None of the patients exhibited any clinical or laboratory evidence of significant systemic disease. Along with discontinuation of the drug treatment, sun protection and topical corticosteroids were the main therapeutic interventions. Two patients were also treated with hydroxychloroquine because these patients’ diseases were initially unrecognized and thought to be idiopathic LE. Most patients had clinically significant improvement within 6 to 12 weeks after discontinuation of treatment with the offending agent (mean, 7.5 weeks). Approximately 40% also showed serologic improvement at the 8-month follow-up. As previously reported,21 we found that the hemagglutination assay was more sensitive than double immunodiffusion for establishing a diagnostic baseline of Ro/SSA positivity and for follow-up monitoring of serologic improvement.

In conclusion, it is critical for clinicians to recognize and appropriately diagnose patients with drug-induced Ro/SSA-positive CLE because the main therapeutic intervention remains the discontinuation of treatment with the offending agent. An accurate history of new medications is necessary in any patient newly diagnosed with Ro/SSA-positive CLE because termination of therapy is essential for resolution of disease if it is drug induced. Patients who present with photodistributed erythema or SCLE lesions and are undergoing treatment with implicated drugs require prompt exclusion of Ro/SSA-positive CLE immunopathologically and serologically. Patients undergoing statin therapy with photodistributed eruption and “myopathy” require careful clinicopathologic correlation because Ro/SSA-positive CLE may mimic dermatomyositis in these cases. All patients treated with any of these implicated medications should be advised about this underrecognized adverse effect.

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REFERENCES


