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A systematic review of drug-induced subacute cutaneous lupus erythematosus

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Summary

The initial appearance of subacute cutaneous lupus erythematosus (SCLE) skin lesions in conjunction with Ro/SS-A autoantibodies occurring as an adverse reaction to hydrochlorothiazide [i.e. drug-induced SCLE (DI-SCLE)] was first reported in 1985. Over the past decade an increasing number of drugs in different classes has been implicated as triggers for DI-SCLE. The management of DI-SCLE can be especially challenging in patients taking multiple medications capable of triggering DI-SCLE. Our objectives were to review the published English language literature on DI-SCLE and use the resulting summary data pool to address questions surrounding drug-induced SCLE and to develop guidelines that might be of value to clinicians in the diagnosis and management of DI-SCLE. A systematic review of the Medline/PubMed-cited literature on DI-SCLE up to August 2009 was performed. Our data collection and analysis strategies were prospectively designed to answer a series of questions related to the clinical, prognostic and pathogenetic significance of DI-SCLE. One hundred and seventeen cases of DI-SCLE were identified and reviewed. White women made up the large majority of cases, and the mean overall age was 58·0 years. Triggering drugs fell into a number of different classes, highlighted by antihypertensives and antifungals. Time intervals ('incubation period') between drug exposure and appearance of DI-SCLE varied greatly and were drug class dependent. Most cases of DI-SCLE spontaneously resolved within weeks of drug withdrawal. Ro/SS-A autoantibodies were present in 80% of the cases in which such data were reported and most remained positive after resolution of SCLE skin disease activity. No significant differences in the clinical, histopathological or immunopathological features between DI-SCLE and idiopathic SCLE were detected. There is now adequate published experience to suggest that DI-SCLE does not differ clinically, histopathologically or immunologically from idiopathic SCLE. It should be recognized as a distinct clinical constellation differing clinically and immunologically from the classical form of drug-induced systemic lupus erythematosus.

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Conflicts of interest
None declared.

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Rubin[1] has pointed out that drug-induced systemic lupus erythematosus (SLE) was first reported in 1952 in association with hydralazine therapy for malignant hypertension. Since then, the induction or exacerbation of clinical features of SLE by drug exposure has been considered predominately within this context.

Drug-induced SLE is dominated by systemic symptoms such as fever, arthritis, myalgias and serositis occurring in association with the production of antinuclear antibodies (ANA) having specificity for histones. Lupus erythematosus (LE)-specific skin changes of any type including subacute cutaneous LE (SCLE) are relatively uncommon in the classical form of drug-induced SLE.[2] Drugs other than hydralazine that have most frequently been implicated as triggers for drug-induced SLE include procainamide, isoniazid, D-penicillamine and quinidine. However, various drugs in different classes have been reported less frequently.

In 1985, Reed *et al.*[3] reported five patients who had not previously experienced features of SLE or cutaneous LE who developed clinically, histopathologically and immunopathologically typical SCLE skin lesions while taking hydrochlorothiazide (HCTZ). The skin lesions in these patients were said to

be indistinguishable from those of idiopathic SCLE and were accompanied by the same autoantibodies (Ro/SS-A and La/SS-B) and HLA type (HLA-DR2/DR3) that had previously been associated with idiopathic SCLE. The SCLE skin lesions in these five patients resolved spontaneously upon discontinuing the HCTZ; however, the Ro/SS-A antibody persisted in all except one patient. After resolution of skin disease activity, one patient was re-challenged with a related thiazide diuretic with reappearance of SCLE skin disease activity that resolved after drug discontinuation. Thus, the concept of drug-induced SCLE (DI-SCLE) was born.

Reed *et al.*[3] speculated that 'this might represent a new type of photosensitive drug reaction in which the photoactive drug may be synergistic with anti-SS-A antibody in producing cutaneous lesions of photosensitive SCLE'. They suggested that thiazides could be involved in enhancing Ro/SS-A antibody-induced keratinocyte cytotoxicity either by promoting Ro/SS-A autoantigen expression on keratinocytes or by enhancing keratinocyte cytotoxicity through direct phototoxicity. They also allowed for the possibility that other photoactive drugs may have similar capacity of inducing SCLE skin lesions.

Since this seminal report in 1985, various drugs in unrelated pharmacological classes have been implicated as triggers for DI-SCLE. With some exceptions, the drugs that have been reported to trigger SCLE lesions are distinct from those that are recognized to trigger drug-induced SLE, probably reflecting fundamentally different underlying disease mechanisms. Several clinical and aetiopathogenetic questions have been raised by the complex array of drugs that have been reported to be capable of triggering SCLE skin lesions. Are the clinical, pathological and laboratory features of SCLE induced by different classes of drugs the same or different? Besides discontinuation of the suspected offending drug, are there other measures that might be of benefit in the management of DI-SCLE? What mechanism(s) might be envisioned to explain the induction of the SCLE subphenotype by such widely differing classes of drugs? We therefore undertook a systematic review of the DI-SCLE published literature, better to address these and related questions.

Materials and methods

Case definitions

The primary case definition for this study is that of DI-SCLE as presented above (i.e. the initial appearance of typical clinical, histopathological, immunopathological and laboratory manifestations of SCLE following the administration of one or more systemically administered drugs).

Case identification

The Medline database was searched via PubMed using the term 'drug induced subacute cutaneous lupus erythematosus' and related searches. All non-English language publications were excluded from this analysis. We assumed that if a case had been accepted as having DI-SCLE by the medical journal's review process, it would be appropriate to include the case in our analysis.

Study design

Each qualifying publication was reviewed and relevant clinical and laboratory data transferred to the following fields of a Microsoft Excel spreadsheet for each patient meeting the case definition for this study: investigator, journal, number of cases, age, sex, race, country, implicated drug(s), time to onset of SCLE, drug challenge, HLA haplotype, family history, complement deficiency, tumour necrosis factor single nucleotide polymorphism TNFα-308, mode of clinical presentation, scarring/nonscarring skin lesions, anatomical distribution, comorbidities, systemic SLE symptoms, result of drug withdrawal with treatment of SCLE lesions, result of drug withdrawal without treatment, presence and pattern of direct immunofluorescence abnormalities, anti-Ro/SS-A, anti-La/SS-B, ANA, antihistone, anti-dsDNA, anti-Sm, autoantibody status after resolution, autoantibody reappearance on challenge, histopathology, presence of photochallenge studies, subsequent development of other clinically significant autoimmune diseases such as SLE or Sjögren syndrome, and proposed or speculated pathogenesis.

Data analysis

We analysed the data in the various fields of the spreadsheet based on whether the relevant information had been provided in the various publications. Several authors reported patients taking more than one drug previously implicated as causative agents of DI-SCLE. For statistical analysis, we attributed the DI-SCLE to the drug that the author of the published report named as the causative drug.

Results

We identified 117 published cases of DI-SCLE. Of the cases that reported patient sex 82 of 114 (72%) were female. The mean age was 58·0 years. When race/ethnicity was reported, 34 of 40 were Caucasian.

Table 1 presents the drugs reported to be capable of triggering SCLE. Other drugs have also been anecdotally implicated as potential triggers of DI-SCLE but have not been formally reported to do so: spironolactone, hydroxychloroquine and glyburide. These suggestions have appeared in reviews, chapters, and/or personal clinical observations by one of the authors.[4]

The results of ANA, Ro antibody, La antibody and histone antibody findings are presented in Table 2. Positive direct immunofluorescence was seen in 62 of the 83 cases that reported such findings (75%).

The mean incubation period for all drug classes combined was 27·9 weeks (range 3 days to 11 years). The median incubation time was 6 weeks. The mean and median overall time

Table 1 Drugs identified as causative of drug-induced subacute cutaneous lupus erythematosus (SCLE) in this report

Antihypertensives	40 of 117 reported cases: 34·2%
Calcium channel blockers	
Diltiazem[7,10]	6 cases
Verapamil[7,8]	5 cases
Nifedipine[7,10,30]	3 cases
Nitrendipine[31]	1 case
Diuretics	
Hydrochorothiazide[3,10,22]	10 cases
Hydrochlorothiazide + triamterene[6]	3 cases
Chlorthiazide[5]	2 cases
Beta blockers	
Oxprenolol[32]	4 cases
Acebutolol[33]	1 case
Angiotensin-converting enzyme inhibitors	
Enalapril[10]	2 cases
Lisnopril[10]	1 case
Captopril[34]	1 case
Cilazapril[34]	1 case
Antifungals	30 of 117 reported cases: 25·6%
Terbinafine[12,14–16,35–37]	29 cases
Griseofulvin[13]	1 case
Chemotherapeutics	10 of 117 reported cases: 8·5%
Docetaxel[38]	3 cases
Paclitaxel[24,38]	3 cases
Tamoxifen[39]	2 cases
Capecitabine[40,41]	2 cases
Antihistamines	9 of 117 reported cases: 7·7%
Ranitidine[42]	7 cases
Brompheniramine[42]	1 case
Cinnarizine + thiethylperazine[43]	1 case
Immunomodulators	8 of 117 reported cases: 6·8%
Leflunomide[9,17,25,44]	5 cases
Interferon α and β[10,45]	3 cases
Antiepileptics	3 of 117 reported cases: 2·6%
Carbamazepine[46,47]	2 cases
Phenytoin[48]	1 case
Statins	3 of 117 reported cases: 2·6%
Simvastatin[10,49]	2 cases
Pravastatin[10]	1 case
Biologics	2 of 117 reported cases: 1·7%
Etanercept[50]	1 case
Efalizumab[51]	1 case
Proton pump inhibitors	2 of 117 reported cases: 1·7%
Lansoprazole[52]	2 cases
Nonsteroidal anti-inflammatory drugs	2 of 117 reported cases: 1·7%
Naproxen[53]	1 case
Piroxicam[26]	1 case
Hormone-altering drugs	2 of 117 reported cases: 1·7%
Leuprorelin[19]	1 case
Anastrozole[18]	1 case
Ultraviolet therapy	2 of 117 reported cases: 1·7%
PUVA[54]	1 case
PUVA and UVB[20]	1 case
Others	4 of 117 reported cases: 3·4%
Bupropion[55]	1 case
Tiotropium[56]	1 case
Ticlopidine[57]	1 case
Hay with fertilizer[58]	1 case

The numbers in the table represent citations to references, and the drugs reported to be capable of also producing photosensitivity skin reactions other than SCLE in otherwise healthy individuals are presented in italics. PUVA, psoralen plus ultraviolet (UV) A.

Table 2 Autoantibodies in drug-induced subacute cutaneous lupus erythematosus

	Ro/SS-A, n/N (%)	La/SS-B, n/N (%)	Antinuclear antibodies, n/N (%)	Histone, n/N (%)
Number reported positive at diagnosis	87/107 (81)	35/73 (48)	84/103 (82)	19/57 (33)
Number reported positive after resolution of rash	28/42 (67)	5/9 (56)	19/23 (83)	3/6 (50): in one case antibody appeared after resolution

to resolution of DI-SCLE after drug discontinuation was 7·3 weeks (range 1–32) and 4 weeks, respectively.

In addition to performing a careful analysis of the various drugs and drug classes that have been implicated as triggers for SCLE, this systematic review gives insight into several questions relating to the management, immunopathogenesis and prognostic significance of DI-SCLE:

1 Does DI-SCLE differ significantly from idiopathic SCLE by virtue of clinical, histopathological, immunological or photobiological features?
2 How long are the incubation and resolution periods for DI-SCLE? And what differences are seen between the various triggering drug classes?
3 Do Ro/SS-A and La/SS-B autoantibodies disappear or remain present after the resolution of DI-SCLE?
4 Are there differences in the molecular specificities of Ro/SS-A and La/SS-B autoantibodies in DI-SCLE compared with idiopathic SCLE?
5 Are histone autoantibodies, the marker of drug-induced SLE, associated with DI-SCLE?
6 Do patients who have experienced DI-SCLE subsequently have a higher risk for developing idiopathic SLE or Sjögren syndrome?
7 What is the pathogenesis of DI-SCLE?
8 What is the optimal medical management of DI-SCLE?

Does drug-induced subacute cutaneous lupus erythematosus differ significantly from idiopathic subacute cutaneous lupus erythematosus by virtue of clinical, histopathological, immunological or photobiological features?

DI-SCLE has previously been thought to present clinically, histopathologically and immunologically in a manner similar to idiopathic SCLE. The clinical descriptions of SCLE lesions in the reviewed reports of drug-induced SCLE cannot be distinguished from those of idiopathic SCLE. Both entities present as outbreaks of erythematous, annular and/or papulosquamous lesions in a characteristic distribution with and without scale, occurring mainly in sun-exposed areas.

Histopathologically, DI-SCLE presents as an interface dermatitis/lichenoid tissue reaction indistinguishable from idiopathic SCLE. This pattern includes focal vacuolization of the epidermal basal layer associated with a perivascular dermal lymphocytic infiltrate.

Immunologically, both entities present with granular deposition of IgM, IgG and C3 in a band-like array at the dermal–epidermal junction. Of the 83 DI-SCLE cases that reported direct immunofluorescence findings, 62 were positive (75%). The direct immunofluorescence findings were most commonly described as granular staining at the dermal–epidermal junction, which is consistent with a lesional lupus band. Lesional lupus band rates for idiopathic SCLE have been reported to range between 60% and 70%.

Ro/SS-A autoantibody rates were not significantly different between DI-SCLE and idiopathic SCLE.

To date, phototesting studies have not been reported to address whether the ultraviolet radiation action spectrum of DI-SCLE is similar to or different from that of idiopathic SCLE.

How long are the incubation and resolution periods for drug-induced subacute cutaneous lupus erythematosus? Do the incubation and resolution periods vary between different triggering drug classes?

We analysed the incubation periods for different drug classes. The most reliable findings came from three drug classes: thiazide diuretics, calcium channel blockers and allylamine antifungals. Thiazide diuretics and calcium channel blockers tended to have the longest incubation period. Review of the literature revealed that thiazides had an incubation time ranging from 6 months to 5 years.[3,5,6] Crowson and Magro[7] reported nine patients on calcium channel blockers, with the mean incubation period being 3·2 years. Kurtis *et al.*[8] reported a case induced by verapamil that incubated for 6 years. However, nitrendipine and nifedipine had shorter incubation periods. Two reported cases showed incubation periods of 3 and 8 weeks, respectively.[9,10] Antifungal medications were at the other end of the incubation spectrum. The average incubation time for terbinafine, which made up 29 of the reported cases, was 5·1 weeks.[11,12] The one case with griseofulvin had an incubation time of 2 weeks.[13] In recent reports, the chemotherapeutic drugs capecitabine and paclitaxel showed rapid onset (days in some cases).

We have analysed the resolution phase of DI-SCLE for the numerous drug triggers identified in this review. With respect to resolution, the majority of cases either resolved spontaneously with no treatment or treatment was given but did not appear necessary for DI-SCLE resolution. There were several reports of unsuccessful treatment before withdrawal of the offending drug. Upon discontinuation of the offending drug,

the lesions typically resolved in a matter of weeks. Nine cases appeared to require active treatment for DI-SCLE resolution: four cases induced by terbinafine,[12,14–16] two of the five reported cases caused by leflunomide,[9,17] one case caused by anastrozole,[18] one by leuprorelin,[19] and one case of psoralen plus ultraviolet A treatment.[20] Active treatments employed will be discussed below.

Do Ro/SS-A and La/SS-B autoantibodies remain present after the resolution of drug-induced subacute cutaneous lupus erythematosus?

The general trend observed was that most patients who were Ro/SS-A or La/SS-B positive did not become negative after DI-SCLE resolution (Table 2). Testing intervals for autoantibodies following drug discontinuation ranged from 6 weeks to 3 years. In some cases the levels of Ro/SS-A autoantibody dropped, but this was inconsistently reported in the cases we reviewed.

In 2004, Arbuckle *et al.* published a landmark article demonstrating that autoantibodies, including Ro/SS-A, typically are present long before the onset of signs or symptoms of SLE. This article describes a crescendo of autoimmunity culminating in clinical illness, providing insight into the mechanism by which the Ro and La antibodies might be expected to remain positive after resolution of SCLE lesions.[21]

Are there differences in the molecular specificity of Ro/SS-A and La/SS-B autoantibodies in drug-induced subacute cutaneous lupus erythematosus compared with idiopathic subacute cutaneous lupus erythematosus?

We were unable to find published data that have addressed this issue.

Are histone autoantibodies significantly associated with drug-induced subacute cutaneous lupus erythematosus?

It is well known that histone autoantibodies are associated with drug-induced SLE. We therefore sought to determine whether histone antibodies might also be associated with DI-SCLE. Data pertaining to histone antibody testing were presented in 57 of the 117 DI-SCLE cases identified (Table 2). One-third of these cases reported the presence of antihistone antibodies. However, there was no mention of the histone subtype specificity (e.g. histone 2A, 2B, 3, 4) of the antibodies that were identified. One report identified antihistone positivity only after resolution of the DI-SCLE skin lesions.[15]

Do patients who have experienced drug-induced subacute cutaneous lupus erythematosus subsequently have a higher risk for idiopathic systemic lupus erythematosus or Sjögren syndrome?

We analysed whether there was a tendency for patients who were diagnosed with DI-SCLE to progress to SLE or Sjögren syndrome. The overwhelming majority of patients who experienced DI-SCLE have not been reported to progress to idiopathic SLE or Sjögren syndrome. However, the follow-up intervals have been relatively short. Farhi *et al.* reported a Caucasian man on terbinafine who, 4 months after remission from DI-SCLE, presented with signs and symptoms of SLE. The patient presented with a malar rash, acute thrombocytopenia, leucopenia, neutropenia and lymphopenia. The patient was Ro (+), ANA (−) with normal complement levels.[16] Goodrich and Kohn[22] reported an ANA+ Caucasian woman on HCTZ who presented 6 months after DI-SCLE resolution with pneumonitis that was presumed to be lupus pneumonitis.

SCLE skin lesions can occur in other clinical settings in which Ro/SS-A autoantibody is seen, such as Sjögren syndrome and rheumatoid arthritis.[23] Our review revealed four patients with Sjögren syndrome who later developed DI-SCLE,[24–26] lending further support to the importance of the 8.1 ancestral haplotype immunogenetic background and Ro/SS-A autoantibody production they both share.[27] The reverse is true as well. It has been reported that up to 43% of patients with DI-SCLE have been observed to develop symptoms of Sjögren syndrome over time.[28] Our review supports this claim as three patients complained of xerostomia and/or xerophthalmia (with no diagnosis of Sjögren syndrome) in conjunction with their skin lesions. Because of the growing amount of evidence, including the results of this study, we feel that in patients with Sjögren syndrome and known Ro positivity, consideration should be given to surveillance for DI-SCLE when prescribing medications that are common triggers of DI-SCLE.

The clinical concept of DI-SCLE is now only two decades old. As there can be a considerable lag between onset of serological abnormalities and clinical manifestations of autoimmune diseases like SLE,[21] it will be interesting to determine whether DI-SCLE might be a gateway into systemic disorders such as SLE and Sjögren syndrome given additional time of observation.

What is the pathogenesis of drug-induced subacute cutaneous lupus erythematosus?

Reed *et al.*[3] in their original description of DI-SCLE pointed out that at that time idiopathic SCLE was thought to relate to Ro/SS-A autoantibody-dependent cell-mediated keratinocyte cytotoxicity. They went on to speculate that thiazides could be involved in the pathogenesis of DI-SCLE by multiple mechanisms: (i) enhancing Ro/SS-A antigen expression, (ii) enhancing epidermal cytotoxicity through direct phototoxicity, and/or (iii) enhancing Ro/SS-A antibody production. While they allowed for the possibility that other photoactive drugs might precipitate DI-SCLE through similar mechanisms, it is now rather difficult to envision a common mechanism by which so many different classes of drugs could trigger DI-SCLE.

The induction of a photosensitivity state is a common feature of many drugs that are now recognized to be triggers of

DI-SCLE. In Table 1, those drugs that are known to be capable of producing a photosensitivity state in healthy individuals or individuals with diseases other than LE have been listed in italics. One possibility is that many drugs that trigger SCLE do so by inducing a photosensitivity state. Such a photosensitivity state might then nonspecifically induce SCLE skin lesions via an isomorphic response (syn. Köebner response) in an individual who is immunogenetically predisposed to developing SCLE. Such a process might be viewed as a 'photopharmacological isomorphic response'. In support of this hypothesis is the now recognized fact that the hallmark humoral autoimmune features of SLE can be present without clinical evidence of SLE for many years prior to the appearance of SLE as a clinical illness.[21] This and other hypotheses concerning the aetiopathogenesis of DI-SCLE need to be systematically tested.

What is the optimal medical management of drug-induced subacute cutaneous lupus erythematosus?

The most commonly used treatments in our systematic review of the literature are topical steroids, oral prednisone, hydroxychloroquine, topical tacrolimus and combinations of the previous treatments. In one particularly difficult case of SCLE induced by terbinafine, the patient's recurrence of SCLE was treated successfully with mycophenolate mofetil.[15]

Discussion

This is the first comprehensive review of DI-SCLE designed to address prospectively a series of questions relating to its clinical management and aetiopathogenesis. It is our hope that the results of this review will better equip clinicians to diagnose and manage DI-SCLE more efficiently. In most cases, DI-SCLE is reversible without treatment once the triggering drug(s) is recognized and withdrawn. However, failing to recognize it as a drug-triggered phenomenon can lead to the risks and costs of overevaluation and overtreatment.

However, we do acknowledge that this retrospective analysis has its limitations. One would be variables related to case identification. Resources were not available to us to have foreign-language case reports/series translated and included in this analysis. Also, analysing the number of cases caused by each drug class raises an important concern. Obviously, there could be publication bias regarding drugs that have been previously reported to cause DI-SCLE as these drugs are no longer novel. This could skew the results, leading to under-reporting of a drug class. However, we felt that practitioners could still benefit from knowing that based on published reports, certain drugs are the most commonly reported to cause DI-SCLE (Table 1). In addition, it is possible that cases that are in reality drug induced but do not clinically resolve after drug discontinuation are under-reported because the association is more difficult to prove.

It would be interesting to know whether the molecular specificities of Ro/SS-A and La/SS-B autoantibodies seen in DI-SCLE are different from those of idiopathic SCLE.

Our literature analysis revealed that patients with DI-SCLE are somewhat older than those with idiopathic SCLE, perhaps reflecting the higher rates of drug use associated with ageing. It would be interesting to know how many of the original cohort of 27 patients with 'idiopathic' SCLE reported in 1979 might have been on drugs now recognized to trigger the clinical expression of SCLE.

In clinical practice it is not uncommon that more than one drug being taken by a patient could be incriminated in producing a hypersensitivity reaction. As there are no clinical or laboratory tests to identify the specific inciting drug in DI-SCLE, it is optimal to discontinue all drugs. If this is not possible, all drugs that are not absolutely essential should be discontinued. In this setting, decision-making concerning which drugs to discontinue is often driven by some form of drug attributability algorithm.[29]

What's already known about this topic?

- Most of the current knowledge relating to drug-induced subacute cutaneous lupus erythematosus is the result of individual case reports and small case series. It is difficult to use these scattered bits of information to guide one in managing new cases of drug-induced subacute cutaneous lupus erythematosus.

What does this study add?

- This manuscript represents a systemic review of the literature designed to prospectively answer a series of questions relating to this clinical subject. The results of this review could be of value to clinicians in managing patients with drug-induced subacute cutaneous lupus erythematosus.

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