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REVIEW

Drug-induced subacute cutaneous lupus erythematosus: a paradigm for bedside-to-bench patient-oriented translational clinical investigation

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Abstract At least 71 patients have been reported in which their otherwise typical subacute cutaneous lupus erythematosus (SCLE) skin lesions were felt to have been temporally associated with the systemic administration of a drug. The mean age of this cohort of drug-induced SCLE (DI-SCLE) patients was 59 years of age which is somewhat older than the mean age of previously reported idiopathic SCLE patient cohorts. Patients had been taking the suspected triggering drug for weeks to years before the onset of SCLE skin lesions. In addition, it was not unusual for 2–3 months to be required for resolution of the SCLE skin lesions following discontinuation of the triggering drug. A relatively large number of drugs representing different pharmacological classes have been implicated in the induction of SCLE. The drug classes that were more frequently encountered were those used for the treatment of cardiovascular disease, especially hypertension. Calcium channel blockers were especially common in this regard. Elderly individuals being treated for hypertension are often taking multiple classes of drugs that have been implicated in triggering SCLE (thiazide diuretics, calcium channel blockers, angiotensin converting enzyme (ACE) inhibitors, beta-blockers). An approach to the management of DI-SCLE is presented. Ro/SS-A autoantibodies tended to remain present in the blood after resolution of drug-induced SCLE skin lesions. A common link between the disparate group of drug structures implicated in triggering SCLE is their tendencies to produce photosensitivity and lichenoid drug reactions. This leads to the speculation that DI-SCLE could represent a photo-induced isomorphic/Köebner response in an immunogenetically predisposed host.

Keywords
Drug-induced subacute cutaneous lupus erythematosus · Bedside-to-bench patient-oriented translational clinical investigation

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Introduction

David Nathan has defined the individual, typically a physician, who performs "patient-based" clinical research as a *patient-oriented translational clinical investigator* (POTCI) [11]. Two subtypes exist within the POTCI persona. One subtype focuses on translating the advances of basic research into improved clinically practices (i.e., rendering advances in basic science into better diagnostics and better treatments). This persona is typically referred to as the "bench-to-bedside" POTCI. In this setting, POTCIs who are conversant with the language and literature of a basic research discipline attempt to "translate" new research insights into better clinical practices for patients.

The other patient-based clinical research subtype is the "bedside-to-bench" POTCI. This is typically a physician scholar who extends her/his professional effort to the generation and publication of new knowledge by studying

patients to whom they personally provide "hands-on" medical care. This is accomplished by careful subphenotyping of disease(s) of interest through critical analysis of epidemiologic, clinical and laboratory information. Clinical specimens such as skin biopsy tissue, serum, DNA/RNA are often collected from patients sharing homogeneous clinical subphenotypes of interest. This material is then examined in a laboratory setting by the POTCI alone or in collaboration with physician scientists and/or basic scientists in order to test a hypothesis that often has been generated by the bedside-to-bench POTCI. Such hypotheses address disease classification, etiology, pathogenesis and/or improved treatment. When dealing with rare/orphan diseases, such clinical information and specimens might be shared with other bedside-to-bench POTCIs having similar interests at other institutions in collaborative multicenter studies.

The concept of subacute cutaneous lupus erythematosus (SCLE) as we understand it today three decades after it's original description in 1979 [18] has resulted largely from the combined efforts of many bedside-to-bench and bench-to-bedside POTCIs around the world since then (contributions reviewed in [3, 12, 16, 17]). The efforts of these workers have established SCLE as a distinctive clinical, histopathologic, and immunogenetic subphenotype recognizable within the mosaic of LE (Fig. 1).

In this presentation we will highlight a clinical facet of the SCLE subphenotype that continues to evolve, drug-induced SCLE (DI-SCLE). A better understanding of this pattern of disease that has been brought to our attention by many clinical scholars and bedside-to-bench POTCIs might contribute to a better understanding of the etiopathogenesis of idiopathic SCLE. A more comprehensive analysis of an extension of this data set through May, 2008 is being published separately [4].

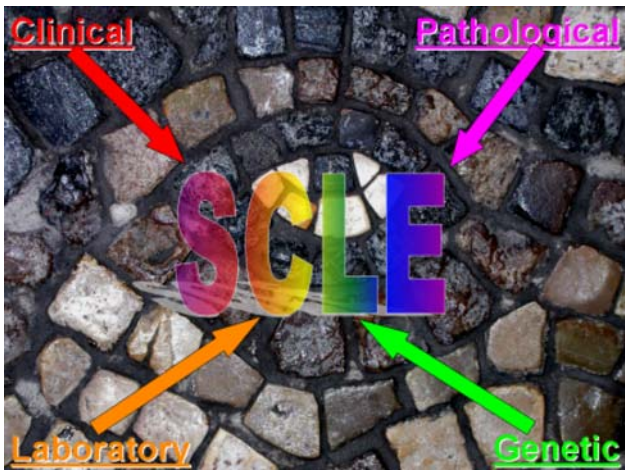

Fig. 1 SCLE as a subphenotype of LE. SCLE can be viewed as a distinctive subphenotype within the mosaic of LE recognizable by its combination of characteristic clinical, histopathologic, and immunogenetic features

History of drug-induced SCLE (DI-SCLE)

In 1985, Reed and coworkers at the University of Colorado reported five patients whose otherwise typical SCLE skin lesions developed while taking hydrochlorothiazide. In all five patients, the SCLE lesions resolved following hydrochlorothiazide discontinuation. SCLE lesions reappeared in one patient that was re-challenged with hydrochlorothiazide. All five patients were positive for Ro/SS-A autoantibodies. Ro/SS-A autoantibodies disappeared in 1/3 patients that were examined after resolution SCLE lesions following hydrochlorothiazide withdrawal. These workers hypothesized that thiazides might potentiate epidermal keratinocyte cytotoxicity and that thiazides might also promote Ro/SS-A antibody production.

However since then, a number of other seemingly unrelated classes of drugs have also been reported to be capable of triggering DI-SCLE. To gain a broader perspective on the epidemiology, clinical and laboratory features, management, and prognosis of DI-SCLE, we performed a systematic review of the published literature in this area through mid 2007.

Definition and epidemiology of DI-SCLE

It should be noted that formal criteria for diagnosing DI-SCLE have yet to be formulated. The strongest evidence linking a drug to the induction of SCLE would be a positive challenge/provocation with the suspected drug after withdrawal of the initially suspected drug had resulted in resolution of the SCLE lesions. However, this has been carried out only rarely in drug-induced SCLE patients. Therefore, our only criterion for including cases of DI-SCLE in this review was the fact that proposed cases had withstood editorial and/or peer review during the publication process.

The large majority of cases were identified through PubMed/Medline searches. The Reference sections of the resulting publications were examined to identify additional cases published in journals not indexed by PubMed/Medline.

Our search strategy identified 71 published cases of DI-SCLE as of June, 2007. Each of these cases was presented as individual case reports or in small retrospective cases series. To date, no population-based data have been presented concerning the epidemiology of DI-SCLE.

The large majority of cases were Caucasian females. The mean age of the DI-SCLE cases identified in this review was 59.5 years. The time range between starting the triggering drug and the first appearance of SCLE lesions (i.e., the "incubation period") was 2 weeks–3.2 years. The mean time to clearance of lesions after the suspected

triggering drug was discontinued was 5.76 weeks with a range of 1-24 weeks (i.e., "resolution period"). There were not enough data reported to determine whether different drug classes exhibited different incubation periods and resolution periods.

Drugs implicated in DI-SCLE

Table 1 presents the various systemic therapeutic agents listed alphabetically by category that our search strategy found to have been reported to be associated with the induction of SCLE skin lesions. Interestingly, almost half of these drugs are primarily used for the treatment of cardiovascular disease, especially hypertension. The individual drug classes most frequently associated with the induction of SCLE were calcium channel blockers and antifungals (especially terbinafine). Of interest in this regard is the fact that a recent case control study demonstrated that chronic eczematous eruptions in the elderly are significantly associated with exposure to calcium channel blockers [5].

To date, no significant differences have been observed in the clinical, histopathologic, immunopathologic, and laboratory features of DI-SCLE and idiopathic SCLE. Ro/SS-A autoantibodies were present in a majority of the DI-SCLE cases in which such data were reported at a rate similar to that seen in idiopathic DI-SCLE. One question of interest in this area is whether Ro/SS-A autoantibodies might disappear after discontinuation of the triggering drug and resolution of the SCLE lesions. Our analysis of this published cohort of DI-SCLE patients indicated that this is not the case. A large majority of patients when re-examined were found to still have Ro/SS-A autoantibodies in their blood following resolution of SCLE skin lesions resulting from drug discontinuation. This is not at all surprising since it has been reported that Ro/SS-A antibodies can be detected in the blood of individuals 5–10 years before they are diagnosed with systemic LE [1]. Virtually no data have been reported to date concerning the molecular subspecificities of Ro/SS-A autoantibodies in DI-SCLE patients. Histone antibodies, the serologic marker of classical drug-induced SLE, were present in less than 50% of the DI-SCLE cases in which such data were reported.

By way of summary, one should consider DI-SCLE in older individuals presenting with SCLE skin lesions for the first time, especially those being treated for cardiovascular disease. Such patients may concurrently be taking medications from multiple pharmacologic classes that have been reported to induce DI-SCLE (e.g., thiazide diuretics, calcium channel blockers, ACE inhibitors, beta blockers). In this setting, it can be very challenging to determine which specific drug(s) might be the key triggering agent(s).

Relationship between DI-SCLE and DI-SLE

It is curious that the classes of drugs that have been reported to induce SCLE have little overlap with those that have traditionally been associated with drug-induced systemic LE [15]. Perhaps this reflects fundamental differences in the pathogenesis of these two patterns of drug-induced LE. This is supported by the facts that the classical form of drug-induced systemic LE rarely includes lupus-specific skin changes such as SCLE and clinically significant internal manifestations of systemic LE have been absent to minimal in DI-SCLE cases reported to date.

Optimal management of DI-SCLE

Management of DI-SCLE involves the immediate treatment of symptoms and elimination of drug trigger(s). Symptomatic treatment with topical and/or systemic anti-inflammatory measures while DI-SCLE lesions remain active is not different from idiopathic SCLE (e.g, topical corticosteroids/nonsteroidal immunomodulators, systemic corticosteroids and/or aminoquinoline antimalarials). Symptomatic treatment can be withdrawn once the DI-SCLE disease activity has abated (this might require 2–3 months following discontinuation of the triggering drug(s)). However, symptomatic treatment of SCLE skin lesions might obscure the ability to determine which drug was responsible after it's withdrawal.

Decisions about which drug(s) to discontinue in the setting of suspected DI-SCLE should ideally be driven by a drug attributability algorithm [14]. Such algorithms have been described in the past, including the Naranjo probability scale [10]. Unfortunately, such an algorithm has yet to be developed for DI-SCLE. The wide range of lag periods between the start of a drug and the onset of SCLE lesions identified in our review dilutes the value of the drug history in such an algorithm. However, medications started after the onset of SCLE lesions can be eliminated from further consideration.

Drug withdrawal strategy is more straightforward when a patient is taking only a single drug that is know to be a trigger for DI-SCLE. However, when an individual is taking two or more such medications, clinical decision making becomes much more challenging. Objective evidence incriminating a specific drug could be very helpful in this setting.

When multiple drug classes capable of inducing SCLE are being taken by a patient, one management strategy would be to coordinate a "drug holiday" (syn. drug vacation, structured treatment interruption) for the patient with the patient's primary care physician. However, such action in the setting of drug treatment for cardiovascular disease

Table 1 Systemic drugs implicated as triggering agents for SCLE

	Photosensitizer[a]	Lichenoid drug reaction[b]
Class frequency ≥ 5% (listed by decreasing frequency of reported class association)		
Antifungals		
Griesofulvin	+	+
Terbinafine	+	
Calcium channel blockers		
Diltiazem	+	+
Nifedipine	+	+
Nitrendipine[c]		
Diuretics		
Hydrochlorothiazide	+	+
Spironolactone	+	+
Antihistamines		
Cinnarazine/triethylperazine[c]		
Chemotherapeutics		
Docetaxel (taxotere)	+	
Beta blockers		
Oxprenolol[c]		
Class frequency ≤ 5% (listed alphabetically)		
ACE inhibitors		
Captopril	+	+
Cilazapril[c]		
Antacids		
Omeprazole		+
Ranitidine	+	
Antieleptics		
Phenytoin		+
Antimalarials		
Hydroxychloroquine	+	+
Immune modulators		
Etanercept		
Infliximab	+	
INF-a	+	+
Lipid lowering		
Pravastatin	+	+
Simvastatin	+	+
NSAIDS		
Naproxen	+	+
Piroxicam	+	+
Sulfonylureas		
Glyburide	+	+
Miscellaneous		
D-penicillamine		+
Insecticides		
Leufonamide		
Procainamide		

[a] Reported to cause photosensitivity in Jerome Litt's *Pocketbook of Drug Eruptions*, 3rd edition [9]

[b] Reported to be capable of inducing a lichenoid drug reaction in Jerome Litt's *Pocketbook of Drug Eruptions*, 3rd edition

[c] Not currently approved for use in the USA and therefore not covered by Jerome Litt's *Pocketbook of Drug Eruptions*, 3rd edition

would have to be monitored very carefully and extended for 2–3 months to account for the prolonged resolution phase of drug-induced SCLE.

A specific triggering agent of DI-SCLE can be retrospectively confirmed by drug challenge/drug provocation following drug withdrawal and resolution of SCLE skin

lesions. This approach is limited by the possibility of the drug-induced disease exacerbation being clinically more severe than the original reaction. In addition, there are medical legal issues that would have to be addressed with such an action in some countries including the USA.

A prospective system for identifying the specific triggering agent would be more useful, especially for patients taking multiple drug classes that are capable of inducing SCLE. A number of in-vitro tests have been proposed to identify specific drugs that might be responsible for an adverse drug reaction in the skin. These include a macrophage migration inhibition tests, lymphocyte toxicity assays, lymphocyte blast transformation tests, and basophil degranulation tests. However, the clinical utility of these assay approaches has not been systematically evaluated and none have been applied to the problem of drug-induced SCLE.

A new assay approach along these lines that might be examined in this regard is a highly efficient in vitro laboratory test that measures cell mediated immune responses in humans using whole blood (e.g, the QuantiFERON-CMI kit [Cellestis]). This test involves stimulation of undiluted whole blood with test antigen(s) (i.e., suspected drug triggers) and a mitogen provided with the kit. T-cell responses are then determined by quantitative measurement of interferon-gamma in plasma by a rapid, single-step enzyme linked immunosorbent assay. Knowing now that LE specific skin lesions such as SCLE exhibit overexpression of interferon-alpha, it might be of interest to adapt this cell-mediated immune kit assay technique for quantifying interferon-alpha as well as interferon-gamma.

Some have advocated photopatch testing as an in-vivo approach to identifying systemically administered drugs that trigger photosensitivity skin reactions [7, 8]. Such protocols have typically employed 10% concentrations of suspected drugs in petrolatum as the patch test reagents with and without subsequent suberythemal UVA exposure to the patch test sites. A variation on this technique is the "photoprick" test in which drug entry into the skin is facilitated by pricking the skin prior to UVA irradiation [2]. Both such testing approaches might be falsely negative in cases in which the DI-SCLE resulted from an immune response to an active metabolite of a drug rather than the intact drug molecule itself. However, as with the above noted in-vitro assays, the clinical utility of in-vivo photopatch testing in photosensitivity states induced by systemic drugs has not been determined. To our knowledge photopatch or photoprick testing with suspected drugs has not yet been reported in the evaluation of DI-SCLE patients.

It might also be of interest to adapt modern cutaneous LE photo-provocation protocols for this purpose. Such protocols typically expose an area of non-lesional skin on the back of patients having cutaneous LE lesions elsewhere on their body with repeated doses of UVB and/or UVA [6]. In variable percentages of patients, skin lesions resembling cutaneous LE will arises in such photo-challenge skin sites within several weeks. In patients suspected of having DI-SCLE, it might be of interest to adapt such protocols by injecting a solution of the suspected triggering drug or its microsomal metabolites into the photo-provocation skin test sites before exposing the test site to UVB/UVA irradiation. By comparing such results to those seen in control sites pre-injected with the drug diluent alone, the potentiating/exacerbating effects of a drug structure on the induction of LE specific skin disease such as SCLE might be objectively examined.

Implications pertaining to the pathogenesis of drug-induced SCLE

Reed et al. [13] in their original description of hydrochlorothiazide induced-SCLE suggested that thiazide specific perturbations of pathogenetic mechanisms of SCLE might account for this clinical association. However, as this review has revealed, any explanation of the pathogenesis of DI-SCLE must account for the fact that a large number of drugs representing a number of disparate pharmacologic classes can trigger DI-SCLE. Even though these triggering drug classes are structurally diverse, might there be some commonality with which they impact cutaneous physiology?

One possibility is drug-induced photosensitivity. As illustrated in Table 1, a majority of the drugs that have been implicated in DI-SCLE have been reported to be capable of producing photosensitive skin reactions. Some of the drug classes that have been implicated in DI-SCLE are well known photosensitizers while others have been implicated in only sporadic case reports. This might justify a speculation that DI-SCLE could be an example of a photo-induced isomorphic (Köebner) response. Stated another way, might an otherwise mundane photosensitive drug eruption be capable of inducing SCLE via a Köebner response in an immunogenetically predisposed host?

Perhaps the cutaneous inflammation produced by a photosensitive drug eruption could perturb the cutaneous innate immune response resulting in increased local class I interferon production by plasmacytoid dendritic cells. Up regulation of interferon-a production and its downstream effects (i.e., CXCL9-11 elaboration with resulting recruitment of CXCR3 cytotoxic T cells) is know to occur in most LTR/IFD skin disorders including cutaneous LE [19]. These and related issues are illustrated in Fig. 2.

It might also be speculated that drugs which are known to produce photo lichenoid eruptions might be more likely to produce DI-SCLE. This hypothesis is also supported by the information presented in Table 1.

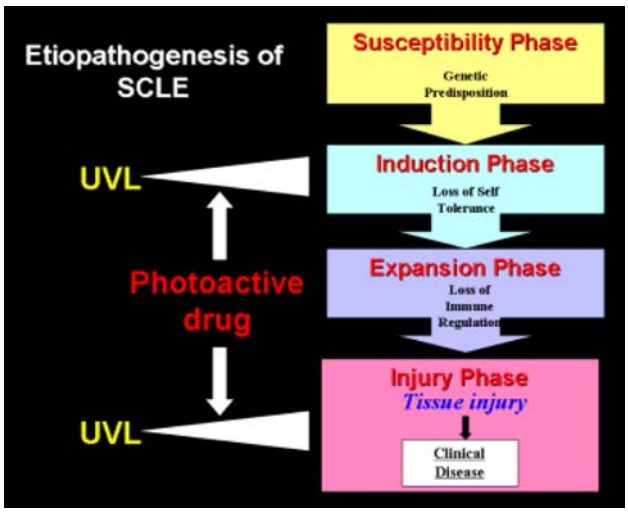

Fig. 2 Possible roles of drug induction in the pathogenesis of SCLE. The etiopathogenesis of a complex human genetic disease such as SCLE can be envisioned as a four temporally linked stages that typically play out over a multiyear time frame: (1) genetic susceptibility, (2) loss of immune tolerance, (3) expansion of autoimmunity, (4) immunologic effector mechanisms causing tissue injury and clinical disease expression. Environmental factors such as UVL could trigger or accentuate the induction/rate of progression of several of these stages. In DI-SCLE, a photoactive drug could possibly accentuate the exacerbating effects of UVL on these pathogenetic stages

Population-based data concerning the epidemiology and optimal management of drug-induced SCLE is greatly needed. As an example, it would be interesting to know if DI-SCLE occurred more commonly in Ro antibody-positive individuals treated with drugs known to trigger DI-SCLE compared to those who are not taking such drugs. In addition, it would be interesting to know what effects the administration of SCLE triggering drugs followed by UVA/UVB light might have on animal models of systemic LE and cutaneous LE.

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Conflict of interest The authors have no potential conflict of interest.

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