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DRUGS AND HORMONES

Drug-induced lupus: an update

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Drug-induced lupus erythematosus (DILE) is a lupus-like illness that has been recognized as an entity under environmentally-induced lupus erythematosus, where other agents such as physical (ultra-violet irradiation), chemical (heavy metals, aromatic amines) and food products (alfalfa sprouts) have been implicated. DILE has been accepted as a side effect of therapy with over 80 drugs since its first description in association with sulfadiazine in 1945. The epidemiology and clinical course of SLE and DILE differ markedly and prognosis is generally favourable in the latter although occasional life-threatening cases have been reported in the literature. Constant pharmacovigilance is crucial for prompt diagnosis and cessation of offending therapy offers the best outcome. This review discusses the clinical presentation, diagnosis of DILE as well as provides an update on postulated pathogenic mechanisms and an overview of implicated drugs. *Lupus* (2006) **15,** 757–761.

Key words: drug-induced; lupus erythematosus

Introduction

Over the past five decades, it has been recognized that certain drugs may exacerbate underlying systemic lupus erythematosus (SLE) or induce a lupus-like illness known as drug-induced lupus erythematosus (DILE) in patients with no prior history. DILE may be considered under the umbrella of environmentally-induced lupus erythematosus, where other agents such as physical (ultra-violet irradiation), chemical (heavy metals, aromatic amines) and food products (alfalfa sprouts) have been implicated. The epidemiology and clinical course of SLE and DILE differ markedly and prognosis is generally favourable in the latter with resolution of the symptoms within weeks once the offending drug has been withdrawn. DILE has been recognized as a side effect of therapy with over 80 drugs since its first description in association with sulfadiazine in 1945.[1] The clinical manifestations may be limited or systemic. This review discusses the clinical presentation, diagnosis of DILE as well as provides an update on postulated pathogenic mechanisms and an overview of implicated drugs.

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Drug-induced lupus erythematosus

Definition

Although there are currently no formal classification criteria for the diagnosis of DILE, it is widely accepted that DILE is defined as the development of lupus-like symptoms (commonly fever, musculoskeletal involvement and serositis) that is temporally related to continuous drug exposure (>1 month) which resolves with cessation of the offending drug. It is usually accompanied by serologic findings of a positive antinuclear antibody (ANA) as well as anti-histone antibodies. Unlike idiopathic SLE, antibodies to dsDNA are rare.[2]

Epidemiology

The age of onset of DILE is generally older; with an equal female to male distribution[3] and has an estimated incidence of 15 000–20 000 cases per year.[4] Whites may be affected up to six times more frequently than blacks and may have more severe manifestations. Certain risk factors have been identified such as the slow acetylator status,[5] HLA-DR4[6] HLA-DR0301,[7] complement C4 null allele[8] and the female gender.[6,9]

Clinical and serologic features

The clinical spectrum of DILE ranges from limited cutaneous involvement to a systemic form that is

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generally mild. The time between drug exposure to onset of symptoms varies from one month to as long as over a decade after initiation of the drug treatment. The onset is generally insidious.[10]

I. Drug-induced systemic lupus erythematosus

Patients commonly present with fever, arthalgia (90%) or arthritis, myalgia (50%) and serositis. These symptoms are usually mild although life-threatening cases have been reported.[11,12] The classic malar or discoid rash, oral ulcers[13] and major organ involvement (renal and neurologic) seen in idiopathic SLE are notably rare in DILE (Table 1). Laboratory findings may include mild cytopenia and an elevated erythrocyte sedimentation rate. Although most patients typically have a positive antinuclear antibody (ANA), the incidence is variable. The ANA pattern is consistently homogenous as the autoantibodies target nuclear histone proteins. Anti-histone antibodies are positive in up to 95% of DILE while anti-dsDNA antibodies are rare; in contrast to idiopathic SLE (Table 1).[14] Longitudinal studies have shown that the ANA and anti-histone titres gradually decline with the resolution of DILE.[15] Another distinguishing feature of ANA in DILE is that these antibodies are not complement-fixing, unlike those in SLE.[16] Finally, it has been demonstrated that various subnucleosome particles within the histone-DNA complex in the cell nucleus, have varying antigenicity across different drugs in DILE.[17,18] For example the (H2A-H2B)-DNA complex is the predominant antigenic particle in procainamide-induced LE. Anti-histone antibodies albeit more prevalent, are however not pathognomonic of DILE as they are found in SLE and have been reported in other rheumatic diseases such as scleroderma, rheumatoid arthritis and undifferentiated connective tissue disease.[19,20] This apparent paradox has led to the postulate that the metabolites of offending drugs have the capacity to non-specifically disrupt central immune tolerance to chromatin which alludes to the pathomechanism of idiopathic SLE as well.[21]

Table 1 Contrasting characteristics of DILE and idiopathic SLE

Characteristics	*DILE*	*SLE*
Age of onset	Older	Child-bearing years
Female : male	1:1	9:1
Clinical course	Remits with drug cessation	Chronic, relapsing
Symptom severity	Generally mild	Mild to severe
Major organ involvement	Rare	Common
Cutaneous involvement	Purpura, erythema nodosum SCLE	Malar, discoid rash, photosensitivity, oral ulcers
Serologic features	ANA (homogenous) Anti-histone (up to 95%) Anti-dsDNA (<5%)	ANA (homogenous, speckled) Anti-histone(up to 50%) Anti-dsDNA (50–70%)

II. Drug-induced subacute cutaneous LE

Drug-induced subacute cutaneous LE (SCLE) is similar to idiopathic SCLE in terms of clinical and serologic characteristics and is less prevalent than the systemic form of DILE. In a retrospective review of 70 patients with biopsy-proven SCLE, 21% had drug-induced SCLE and the most commonly implicated drugs were namely antihypertensive agents (thiazide diuretics, angiotensin-converting enzyme inhibitors and calcium-channel blockers).[22,23] More recently, terbinafine, an oral anti-fungal agent;[24] bupropion, an antidepressant[25] and acebutolol, a beta-blocker[26] have been described as probable offending agents.

Drugs exacerbating underlying SLE

In DILE, years of exposure to steady-state levels of the offending drug are required for the development of this syndrome. Conversely, exposure to low levels of certain drugs for relatively short periods leads to exacerbation of underlying SLE. A wide variety of drugs have been implicated in causing lupus flares and these include antibiotics particularly sulfonamides,[27] anticonvulsants[28] and non-steroidal anti-inflammatory drugs[29] and estrogens. The results of a recent multicentre SELENA trial (Safety of Estrogens in Lupus Erythematosus, National Assessment) have helped to clarify the controversy over exogenous hormones and lupus flare risk. It demonstrated that the use of oral contraceptives in premenopausal women with stable or inactive SLE was not associated with an increased flare risk. In the postmenopausal arm, short course hormone replacement therapy was associated with a significantly increased risk of mild to moderate lupus flares ($P < 0.01$). In both arms, women with a history of thrombosis or high titre antiphospholipid antibodies were excluded.[30,31] Nonetheless, caution should be exercised in the use of exogenous hormones in such patients.

Pathogenesis of DILE

The pathomechanisms in drug-induced lupus is unlike classical drug hypersensitivity reactions for several reasons:[21] first, it lacks drug-specific T-cells or antibodies and the target autoantigens are not directly affected by the offending drug. Second, the time

course for the development of DILE tends to be much slower than that of classic drug hypersensitivity. Furthermore, reintroduction with a lupus-inducing drug is not associated with memory of prior exposure if systemic autoimmunity had normalized. Finally, the duration of exposure and drug dose affects the likelihood of development of DILE. Four main mechanisms have been hypothesized in the literature to date:[21,32]

Hapten hypothesis

Either the drug or its metabolite binds to protein (hapten), thus making it 'foreign' and incites an immune response against the hapten or possibly self antigens by virtue of molecular mimicry or antigen processing, resulting in presentation of cryptic antigens.[33]

Direct cytotoxicity hypothesis

Certain reactive drug metabolites may directly cause cell death via a non-immune mediated process.[34,35] This has been demonstrated a wide variety of lupus-inducing drugs in vitro. However, this process cannot entirely explain the immune perturbations in DILE. Hence, it has been postulated with a paucity of evidence that drug metabolites also alter degradation and clearance of apoptotic cells which eventually leads to the loss of tolerance to self antigens.

Lymphocyte activation hypothesis

Murine splenocytes exposed to procainamide or hydralazine in vitro demonstrated an increased proliferative response to autologous antigen-presenting cells without the need for cognate antigen and promoted B cell differentiation in antibody-secreting cells. Adoptive transfer of such cells induced a lupus-like syndrome in mice.[36]

Disruption of central immune tolerance

Murine models have shown that intra-thymic injections of lupus-inducing drugs resulted in a delayed but sustained production of anti-chromatin antibodies. It was subsequently demonstrated that these drugs interfered with the establishment of tolerance to endogenous self-antigens that are normally presented by the MHC to thymocytes. Hence mature T-cells are capable of undergoing spontaneous activation when encountering similar self antigens in the periphery.[37,38]

Drugs implicated in DILE

These can be divided into three main groups according to the likelihood of causing DILE based on the level of evidence available in the literature[2] (Table 2).

Group I: Definite association based on controlled studies confirming its pathogenic role in inducing DILE.

Group II: Probable association based on large series or cohorts consistently reported.

Group III: Possible association with a few case reports.

An exhaustive review of these drugs can be found in a recent publication by Sarzi-Puttini *et al.*[2]

Drugs deserving special mention

Historical drugs: hydralazine/procainamide

These are classic 'prototypic' drugs that cause DILE. Hydralazine was first introduced as an anti-hypertensive agent in 1952 and was soon recognized as a lupus-inducing drug. Patients who are slow acetylators and possess HLA-DR4 are at particular risk of developing DILE. Approximately 10% of patients on this agent develop DILE and a quarter manifest cutaneous lesions.[39] The first case of procainamide-induced DILE was reported 10 years after its introduction in 1951. The incidence of ANA positivity varies between 50–90%. The onset of DILE occurs between three months to two years of constant exposure.

Anti-rheumatic drugs: minocycline/sulphasalazine/D-penicillamine/biologics

The role of biologics in DILE will not be covered in this review. To date up to 80 cases of minocycline-induced

Table 2 Drugs implicated in the development of DILE

Definite	*Probable*	*Possible*	*Recent case reports*
Hydralazine	Sulphasalazine	Antibiotics	Infliximab
Procainamide	Anticonvulsants	Non-steroidal anti-inflammatory agents	Etanercept
Isoniazid	Anti-thyroid	Antihypertensives	Interleukin-2
Methyldopa	Statins	Lithium	Zafirlukast
Quinidine	Terbinafine	Interferons	Clobazam
Minocycline	Penicillamine	Gold salts	Tocainide
Chlorpromazine	Fluorouracil agents		Lisinopril
	Hydrochlorthiazide		Bupropion

Adapted from Sarzi-Puttini *et al.*[2]

autoimmune syndromes have been reported.[40] By far, the commonest manifestations have been DILE and hepatitis. A large nested case-controlled study confirmed an 8.5-fold increased relative risk of developing DILE compared to non- or past users of tetracyclines.[41] Apart from the typical DILE features, minocycline-induced DILE has unusual features including cutaneous (Raynaud's, polyarteritis nodosa, erythema nodosum) and hepatic (steatosis, allergic) manifestations and is rarely associated with positive anti-histone antibodies.[42] The link between sulphasalazine and DILE has been more controversial. Prior reports have suggested an association;[43] however a recent prospective randomized study of 200 rheumatoid arthritis patients followed up over five years revealed that sustained therapy with sulphasalazine did not confer an increased risk of developing DILE.[44] D-penicillamine is a chelating agent that is largely used for the treatment of Wilson's disease. Its use in scleroderma and rheumatoid arthritis has declined in past years. Nonetheless, there have been several case reports citing its possible association with DILE. Unique features described in this setting are that of renal involvement as well as the presence of positive anti-dsDNA and hypocomplementemia.[45]

Commonly used drugs

By virtue of its widespread use, the possibility of the following drugs inducing lupus-like syndromes should be borne in mind:

Antiplatelet agents. Ticlopidine has been recently described in 2002 in a series of four cases.[46]

Antihypertensives. Beta-blockers, most recently acebutolol have been implicated in causing SCLE.[26] Angiotensin-converting enzyme inhibitors (DMIT) have also been named as offending agents. Interesting lisinopril-induced DILE is associated with a negative ANA but positive antihistone antibodies.[47]

Statins. There have been several reports linking various statins (fluvastatin, lovastatin, recently atorvastatin). The clinical manifestations differ from the usual DILE in that cases of pneumonitis, ARDS (acute respiratory distress syndrome), cutaneous (erythema multiforme, Raynaud's, periungual erythema) have been described.[48]

Conclusions

Drug-induced lupus is a reversible lupus-like condition due to exposure to over 80 prescribed drugs to date. Its symptomatology is generally mild to moderate with resolution of both clinical and serologic features over time following drug cessation. The overall prognosis remains favourable although occasional life-threatening cases have been reported in the literature. In these severe cases, transient therapy with corticosteroids may be required. Hence, constant pharmacovigilance for prompt diagnosis as well as cessation of offending therapy offers the best outcome.

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