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Drug-induced Lupus Syndrome

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Abstract

DIL is an autoimmune mediated vasculitis against certain drugs. Such drugs may induce autoantibodies in some patients leading to a clinical syndrome similar to systemic lupus erythematosus. Over 100 drugs with mostly hydralazine, procainamide, quinidine, isoniazid, and diltiazem may often cause increased levels of ANA in serum while some patients with these antibodies may develop clinical symptoms of SLE such as rash, serositis, or arthritis suggesting drug-induced disease. Although DIL and SLE share clinical similarities that may lead to a diagnostic dilemma, these two entities have crucial disparities in pathogenetic, immunologic and clinical features. DIL occurs due to the interactions between the drug and DNA or histones that make them immunogenic. DIL is rare but recognition of this syndrome clinically and serologically is crucial because DIL resolves completely within few weeks after withdrawal of the causative agent. Prompt withdrawal is required because continued use may lead to life-threatening severe cases. This article reviews the pathogenetic mechanisms, clinical manifestations and brings up to date the diagnosis with approach to treatment of DIL.

Keywords: Vasculitis; Pathogenetic; Autoantibodies; Lupus; Serositis

Introduction

Drug-related lupus refers to the development of lupus like syndrome upon exposure to certain drugs. These patients usually present with fewer than four SLE criteria. A temporal association between the culprit drug ingestion and symptom development is required. There is rapid resolution of clinical features after withdrawal of the agent while autoantibodies may persist up to one year. A wide variety of drugs have been implicated in the development of DIL [1,2]. Over the past five decades, it has been recognized that certain drugs may exacerbate underlying systemic lupus erythematosus or induce a lupus-like syndrome known as drug-induced lupus erythematosus (DIL) in patients with no prior history. It may take months or years for DIL to develop after treatment with certain drugs, usually antihypertensives, antibiotics, and anticonvulsants. Hydralazine, procainamide, quinidine, isoniazid, diltiazem, and minocycline are the most common agents. Antinuclear antibody (ANA) and anti-histone antibodies are frequently positive [1-6]. The epidemiology and clinical course of SLE and DIL differ markedly. Prognosis is generally favourable in the latter with resolution of the symptoms within weeks once the offending drug has been withdrawn [7,8]. DIL has been recognized as a side effect of treatment with over 100 drugs since its first description in association with sulfadiazine in 1945 [9]. DIL was later reported in 1953 in patients taking hydralazine [10]. Risk of developing DIL is diverse among different drugs, most common with procainamide (20%), hydralazine (13%), anti-TNF (0.2%), and minocycline (0.05%) [1-6]. Care must be taken to correctly diagnose DIL and differentiate it from other autoimmune diseases, especially from systemic lupus erythematosus. Because DIL may lead to severe and fatal outcomes this syndrome should be recognized promptly for the withdrawal of the causative agent. Cessation of the offending drug offers the best outcome and no treatment is usually necessary. DIL and SLE share similar clinical and laboratory features (Figure 1).

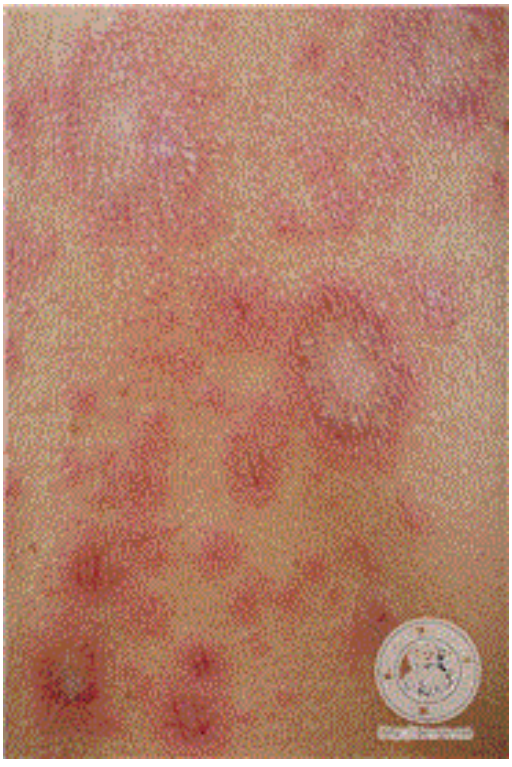

Figure 1: Cutaneous involvement in DIL

They are both autoimmune based diseases but have different pathogenetic mechanisms. Pathogenesis of DIL is not completely understood but a genetic susceptibility may be decisive, as it is the case with procainamide or hydralazine [4-7]. This review discusses the

clinical presentation, diagnosis of DIL and provides an update on postulated pathogenic mechanisms with an overview of the implicated drugs.

Drug-induced Lupus Erythematosus

Definition

Currently, there are no stringent benchmarks for DIL and no definitive criteria exist for the final diagnosis of DIL. The syndrome is defined as the development of lupus-like symptoms that is relevant with continuous drug exposure, usually one month, which resolves with cessation of the offending agent for at least three months. Recurrence of symptoms with re challenge has been proposed as a diagnostic paradigm. The symptoms are usually related to musculoskeletal involvement and serositis. ANA and anti-histone antibodies are positive in most of the patients while unlike from SLE, antibodies to dsDNA are rare [1,4,5].

Epidemiology

Approximately 10% of the 500,000 lupus erythematosus cases in the United States develop due to DIL. Patients with DIL are older, age between 50-70 years, than those SLE patients with an average age 29 years at diagnosis. Older patients are more susceptible to DIL while SLE is most frequent in young adults. The estimated incidence is 15000-20000 per year. There is no statistically significant difference between the prevalence of male and female patients [1-7]. SLE has a considerably higher frequency in females. Whites are affected up to six times more frequently than blacks who present with more severe symptoms (Table 1). Certain risk factors such like the slow acetylator status, HLA-DR4 HLA-DR0301, and complement C4 null Although the female gender have been identified as a risk factor for DIL the prevalence between male and female patients may be considered as negligible [8-14].

Pathogenetic mechanisms

SLE is an idiopathic while DIL is drug induced autoimmune disease. The common point in pathogenesis is the production of autoantibodies against the patient's own tissues. Infectious agents like a virus or bacteria may provoke an immune response cross-reactive with self antigens. Molecular mimicry between antibodies directed against these infectious agents and self-antigens leading to immune cross-reactivity are incriminated for the development of lupus erythematosus [15-17]. Autoantibodies produced against these foreign antigens in turn attack the patient's own tissues. On the other hand, autoantibodies causing DIL are thought to be generated by a similar mechanism which occurs as a reaction to certain drugs. Research suggests that DIL and SLE may have similar but distinct pathogenetic mechanisms [1-3,18-20]. In summary, for DIL the provocative stimulus leading to an immune-mediated vasculitic reaction is the culprit drug whereas it is the infectious agent in SLE. Mechanisms of DIL are diverse. Pathogenesis is related to drug metabolism and the interaction of drug metabolites with an altered immune system. Genetic predisposition, epigenetic phenomena, drug metabolism, drug activation of lymphocytes, TNF-alpha inhibition may be effective in pathogenesis [1-6]. Drug characteristics leading to autoantibody formation are uncertain, but several mechanisms have been suggested. Metabolites of the drug exposed to oxidative metabolism act as a substrate for myeloperoxidase after an oxidative reaction. Myeloperoxidase is activated in polymorph nuclear neutrophils and this interaction leads to formation of reactive metabolites directly affecting the lymphocyte function in the thymus. This reaction damages central T-cell tolerance to the patient's own tissues and regenerates autoimmune T cells against them [4,21,22]. While lupus-inducing drugs undergo oxidative metabolism analogous non–lupus-inducing drugs go through an oxidative metabolism. Reactive metabolites of procainamide injected into the mouse thymus have been shown to result in lupus-like autoantibodies. This process may take a long time, months to years of drug exposure, for symptoms to arise, unlike drug hypersensitivity reactions [6,23,24].

Clinical feature	SLE	DIL
Gender (F/:M)	9:01	1:01
Usual age	20-40	50-70
Race	Affects blacks more	Affects whites more
Symptom severity	Mild to severe	Usually mild
Fever/malaise	40-85%	40-50%
Arthralgia/arthiritis	75-95%	80-95%
Cutaneous findings	>75%	~25%
Cutaneous involvement	Purpura, erythmea nodosum	Malar, discoid rash, photosensivity, oral ulcers
Rash (all)	50-70%	10-30%
Rash (discoid)	20%	Rare
Rash (subacute cutaneous)	58%	20-40%
Rash (malar/acute cutaneous)	42%	2%
Raynaud's	35-50%	<25%
Pleuritis/pleural effusion	16-60%	10-50%
Pulmonary infiltrates	0-10%	5-40%
Pericarditis	6-45%	2-18%
Hepatomegaly/ splenomegaly	10-45%	5-25%
Renal involvement	30-50%	0-5%
CNS/neurologic involvement	25-70%	0-2%
Hematologic	Common	Unusual
Clincal course	Chronic, relapsing	Remits with drug cessation

Table 1: Clinical characteristics of SLE and DIL patients

Diminished T-cell methylation leads to an overexpression of lymphocyte function–associated antigen (LFA-1). T cells with hypomethylated DNA turn into an autoreactive form and this process results in antibody formation. This mechanism leads to cutaneous ultraviolet flares of lupus erythematosus [21-26]. Another theory is that the genetic differences in an individual's P450 system causes different metabolization of drugs that lead to the generation of toxic

metabolites facilitating autoimmunity [23-25]. Predisposing factors for DIL include a slow drug-acetylator phenotype and advanced patient age. Slower acetylation may play a role in a greater predisposition for elderly persons to develop DIL [27,28]. Higher incidence of DIL in older subjects is may probably be related to decrease metabolic clearance together with increased drug use in these subjects.

Clinical features

Symptoms: Symptoms and the clinical profile of DIL vary greatly and may range from limited involvement to severe systemic or fatal disease. DIL shares many clinical features of SLE and patients have frequently one or more clinical SLE symptoms like arthralgias, lymphadenopathy, rash, or fever with prior history of autoimmune disease. Rash often develops in the sun exposed areas as a polycyclic, scaling, and erythematous form. Half of the patients have constitutional symptoms of fever, weight loss, and fatigue while most of the patients have severe non-inflammatory joint pain but synovitis is rare. Arthralgia frequently occurs as the only symptom [29-31]. Patients may have fever, arthalgia or arthritis, and serositis. DIL patients may also present with myalgias. Common manifestations include malaise, weakness, arthralgias, myalgias, and serositis. The symptoms of DIL are usually mild. The classic malar or discoid rash, oral ulcers, and major organ involvement of SLE are uncommon in DIL. Pleural effusions or pericarditis may occur [1,3,6,8]. Such effusions may be severe enough to warrant a differential diagnosis. Clinical and serologic features may vary according to the specific drug used. Pleuritis develops in 50% of patients with DIL from procainamide, in 22% from quinide, and less than 1% from minocycline. Transaminase abnormalities occur in approximately half of the DIL patients due to minocycline while this is rare in procainamide or quinide induced DIL. Pleuritis, pericarditis, pleural effusions, and pulmonary infiltrations are particularly seen in patients using procainamide. In case of coexisting diseases like heart failure, the diagnosis becomes a challenge for the clinician. Hydralazine-induced DIL may lead to severe and fatal outcomes. Nonspecific drug rashes may occur in DIL. Discoid lupus lesions are almost exclusively a feature of SLE [1,2,6,7]. The time interval between drug commitment and symptom appearance is usually three weeks while it may take two years for clinical manifestations to occur. It is usually one month. Drug-associated exacerbations of SLE and typical drug hypersensitivities should be evaluated in the differential diagnosis. Clinical recovery is usually rapid when the drug is discontinued. Antinuclear antibodies and other serologic markers slowly decrease toward more normal levels [7,32-34]. Features of SLE like overt nephritis, hematologic, and neurologic disease are very rare in DIL [1-3].

Antibodies tend to attack double-stranded DNA in lupus erythematosus. Antinuclear antibodies with homogeneous patterns are produced by procainamide, isoniazid, timolol, hydralazine, and phenytoin. In contrast, speckled antinuclear antibody patterns are associated with anti-SSA/Ro antibodies, which can be produced in response to thiazide diuretics such as hydrochlorothiazide [36-39]. The antibodies also tend to attack histones in DIL. Antihistone antibodies are present in more than 75% of patients with DIL induced by hydralazine and procainamide. An example of an antihistone antibody that is often implicated in DIL is immunoglobulin G. Antihistone antibodies are much more likely to indicate DIL but they can also appear in as many as 50% of patients with SLE (Table 2). In persons with DIL, anti-Sm antibodies are rare [31,34].

Laboratory feature	SLE (%)	DIL(%)
ANA	95-98	95-100
Anti-dsDNA	50-80	<5
Anti-Smith	20-30	<5
Anti-RNP	40-50	20
Antihistone	60-80	90-95
Low complement levels	40-65	0
Anemia	30-90	0-46
Leukopenia	35-66	2-33
Positive Coomb's test	18-65	0-33

Table 2: Laboratory features of SLE and DIL

Involvement of these systems indicates SLE (Table 1). High rates of glomerulonephritis ranging between 5% and 10%, may occur in hydralazine-induced DIL and rare cases of death from renal involvement have been reported [7,8,11]. Classical manifestations of SLE like malar or discoid rash, oral ulcers, and major organ involvement, renal or neurologic, are also notably very unusual in DIL [32-34]. Current data suggests that subacute cutaneous cases of SLE (SCLE) may be drug-induced. Drug-induced etiology should be considered in such cases. Skin changes usually occur in 4 to 20 weeks after drug exposure Systemic symptoms are rare in these patients but serositis may occur. It is difficult to differentiate between idiopathic and SCLE.

Biochemistry: There are no definitive or specific criteria for the diagnosis of DIL. Laboratory findings may reveal mild cytopenia and an elevated erythrocyte sedimentation rate. Anemia is present in most patients with SLE but is rare in DIL. Blood urea nitrogen (BUN) and creatinine should be assessed for evaluation of renal disease in both SLE and DIL. Complement levels are often reduced in persons with SLE, whereas the complement levels are within the normal reference range in DIL patients [5,7]. Liver function tests are performed to evaluate for hepatic involvement. Urinalysis is done to evaluate for hematuria and **proteinuria**. Chest X-ray and CT are performed to show pulmonary infiltrates or pleural effusions while echocardiography is done to rule out pericarditis [5,29,34].

Serology: Most patients typically have a positive ANA. Although the incidence is variable it may reach %100 (Table 2). The ANA pattern is consistently homogenous because the autoantibodies target nuclear histone proteins. ANAs should be present to diagnose DIL. However, the presence of ANA without accompanying a clinical profile is not sufficient for diagnosis therefore does not constitute a criteria for drug withdrawal [1,2]. Anti-histone antibodies are positive in up to 95% of DIL while anti-dsDNA antibodies are rare; in contrast to idiopathic SLE. Antinuclear antibodies usually appear in a homogeneous pattern in 90% of patients with lupus erythematosus. In DIL the prevalence of anti-ssDNA is higher [31-35]. This is a major difference from SLE (Table 2).

Pathology: Cutaneous and renal biopsies are indicated if involvement is suggested. Skin biopsy and direct immunofluorescence typically reveal findings that are indistinguishable from those seen in SLE. Histologic examination reveals variable epidermal atrophy, basal

vacuolar degeneration, apoptotic or dyskeratotic keratinocytes, and lymphocytic interface dermatitis [40]. Eosinophilic infiltration indicates and existence of eosinophils on skin biopsy implies DIL or SCLE. Immunofluorescence histopathology reveals granular deposition of IgG at dermoepidermal junction, lymphohistiocytic interface dermatitis, and apoptosis basal vacuolization in both SLE and DIL [1,2,35-38,41,42]. Upon withdrawal of the culprit drug in a patient with a previously normal immune system DIL patients show rapid clinical improvement. There are no specific criteria for the diagnosis of DIL. On the other hand, excluding underlying autoimmune disease is not a simple process. Strict and regular clinical or serologic evidence of DIL is not invariably present, even in rare cases of fatal DIL. Patients have serologic and clinical findings that may normally indicate SLE but in fact they may have DIL [43-45]. The symptoms of both drug-induced SLE flares and DIL are temporally related to drug exposure, and these two conditions have similar manifestations, thereby posing difficulties in differential diagnosis (Figure 2).

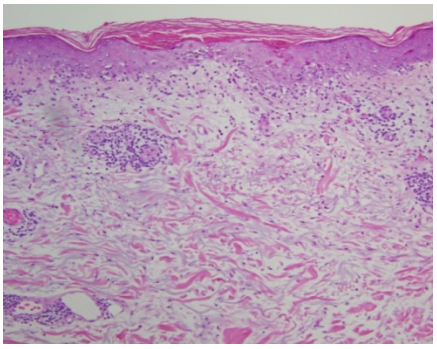

Figure 2: Drug-induced subacute lupus erythematosus: slight parakeratosis, with mild epidermal atrophy, liquefaction of the basal layer, perivascular and periadnexal lymphocytic infiltration

Diagnosis of DIL depends upon the following criteria: one or more clinical symptoms of SLE like fever, arthralgia's, lymphadenopathy, or rash should have occured; before using the culprit drug a history of SLE should not be present; positive antinuclear antibodies; drug commencement interval is between three weeks to two years prior to the clinical picture; and clinical improvement should be rapid when the offending agent is withdrawn. On the other hand, serologic markers and antinuclear antibodies follow a slower course toward baseline levels [29,31,33]. DIL may be considered as a misnomer because the symptoms, clinical and laboratory findings of DIL overlaps frequently leading to confusion in diagnosis. As we have stated in a previous case report drug-induced vasculitis (DIV) would be a more appropriate term than DIL to describe this syndrome [45]. Because DIV reveals similar aspects with other vasculitides and not only with SLE. Second, in some patients the syndrome arises with only cutaneous findings. And, third the laboratory findings overlap with all vasculitides [46]. New drugs are continuously developed and become available for clinical use every day. It is important to recognise that drugs used in other specialties may induce DIL and vigilance on making a diagnosis is the key. Consequently, clinicians should be aware of the new drugs and their potential to cause DIL in every patient.

Conclusions

Drug-induced lupus is a reversible lupus-like condition due to exposure to over hundred drugs. Its symptomatology is usually mild to moderate. Clinical symptoms and serologic features return to normal after the drug is withdrawn. The prognosis is favourable but life-threatening or severe cases with fatal outcomes have been reported. In such patients, therapy with steroids and immunosuppressive agents may be required. Awareness and diligence for certain drugs as well as cessation of the offending agent offers the best outcome. The most important and preliminary step for treatment is to stop the trigger drug as soon as possible. Three to twelve months may be required for complete resolution of the clinical picture. There are no strict criteria or identification test to determine the culprit drug other than noting improvement when the drug is ceased. Reapperarence of the clinical picture within two days with the commitment of the same drug is another clue for diagnosis. The clinical picture and the symptoms show resolution within weeks of drug withdrawal but recovery may take as long as one year. Blood tests return to normal more slowly than the symptoms. In most cases, no specific treatment is required as the drug-induced LE is usually mild and resolves with drug withdrawal but severe complications with fatal outcomes may occur if not recognized. Patient history is the most crucial initial step for diagnosis. Clinicians should bear in mind that drug induced underlying SLE execarbation must be discriminated from DIL syndrome because they share similar clinical and laboratory features but treatments are completely different. The manifestations of DIL also vary according to the specific drug exposure. This is another crucial point to be considered in the diagnosis of drug-induced lupus. In summary; presence of lupus symptoms, use of a culprit drug over three weeks to two years prior to clinical picture, prompt recovery upon drug withdrawal and reappearance of symptoms with rechallenge are considered as the diagnostic criteria of drug-induced lupus. DIV appears to be a more precise and a better term for this syndrome.

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