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REVIEW ARTICLE

Drug-induced lupus erythematosus

Lúpus eritematoso induzido por fármacos

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Abstract

Drug-induced lupus erythematosus is an autoimmune disease with unexpected onset after treatment with certain drugs. Clinically, this disease is very similar to idiopathic lupus erythematosus, although its manifestations are typically milder. In addition, the laboratory and histological changes of the induced forms are also not significantly different from the idiopathic condition, sometimes making the diagnosis of the drug-induced form a challenge for clinicians. This entity has been gaining relevance in the clinical setting and the number of drugs associated with it has been increasing, mainly due to the emergence of new biological therapies with a strong causal link with drug-induced lupus, such as tumor necrosis factor-alpha inhibitors. However, there are still no universally accepted diagnostic criteria to identify this disease, and information about its pathophysiology is still somewhat scarce, making it difficult to predict the most likely culprit drugs before there are enough reports to establish a strong link. In addition, although some risk factors have shown susceptibility for certain individuals, they are not yet fully understood. Given the possibility of disease reversal by the withdrawal of the offending drug, it is extremely important to be aware of the possible implication of a drug in the pathogenesis of this disease, and for clinicians who approach patients with lupus manifestations, particularly cutaneous manifestations, it is mandatory to look for the onset of new drugs used by the patient. This review will systematize the current knowledge about this drug-induced lupus, in terms of pathophysiology, clinical, histopathological, and laboratory manifestations, diagnosis, and treatment, as well as the most commonly implicated drugs.

Keywords: Drug-induced lupus erythematosus. Cutaneous lupus erythematosus. Subacute cutaneous lupus erythematosus. Chronic cutaneous lupus erythematosus. Anti-TNFα. COVID-19.

Resumo

O lúpus eritematoso induzido por fármacos (LEIF) é uma doença autoimune com aparecimento inesperado após o tratamento com determinados fármacos. Clinicamente, é muito semelhante ao lúpus eritematoso idiopático, ainda que as suas manifestações sejam tipicamente mais leves. Adicionalmente, as alterações laboratoriais e histológicas das formas induzidas também não são significativamente diferentes dos quadros idiopáticos, tornando, por vezes, o diagnóstico da forma induzida por fármacos um desafio para os clínicos. Esta entidade tem ganho cada vez mais relevância no contexto clínico e o número de fármacos associados tem vindo a aumentar, principalmente devido ao aparecimento de novas terapias biológicas com forte ligação causal com o lúpus induzido por fármacos, como os inibidores do fator de necrose tumoral alfa (anti-TNFα). Contudo, ainda não existem critérios de diagnóstico universalmente aceites para a identificação desta doença e a informação

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acerca da sua patofisiologia ainda é algo escassa, o que torna difícil de prever os fármacos mais prováveis de a causar antes que haja número suficiente de relatos para estabelecer uma ligação. Além disso, apesar de já terem sido propostos alguns fatores de risco associados a uma maior suscetibilidade em alguns indivíduos, estes ainda não estão completamente esclarecidos. Face à possibilidade de reversão do quadro após a suspensão do fármaco, o alerta para o possível contributo de fármacos na patogenia de lúpus eritematoso é de extrema importância e deve estar presente no diagnóstico diferencial dos clínicos que abordam doentes com manifestações lúpicas, nomeadamente cutâneas, e que iniciaram novos fármacos. Nesta revisão far-se-á uma sistematização do conhecimento atual acerca do lúpus eritematoso induzido por fármacos, em termos de patofisiologia, manifestações clínicas, histopatológicas e laboratoriais, diagnóstico e tratamento, assim como os fármacos mais comummente implicados.

Palavras-chave: Lúpus eritematoso induzido por fármacos. Lúpus eritematoso cutâneo. Lúpus eritematoso cutâneo subagudo. Lúpus eritematoso cutâneo crónico. Anti-TNFα. COVID-19.

Introduction

Drug-induced lupus erythematosus (Di-LE) is an autoimmune phenomenon[1] that can affect the skin and/or multiple body systems, with a phenotype typically similar to idiopathic lupus erythematosus (LE). It occurs after chronic exposure to a particular drug (usually over months or years of use) and tends to resolve after drug discontinuation[2]. This entity has been gaining more and more relevance in clinical practice, currently considered to represent approximately 15% of all causes of LE[3].

As with idiopathic LE, Di-LE can be classified into drug-induced systemic LE (Di-SLE) and drug-induced cutaneous LE (Di-CLE), presenting either as the subacute or chronic subtype[4]. The differential diagnosis between drug-induced and idiopathic cases can be a challenge since clinical aspects, serology, and histopathology are identical[5]. However, they tend to differ in the extent to which they involve different organs and in their clinical course, since Di-LE usually presents as a milder clinical picture with fewer complications[2].

Drugs can either unmask clinically silent LE, induce LE exacerbations in a patient that has already been diagnosed (as reported with abatacept[6]), or trigger a "lupus-like" syndrome, which is the most frequent case[2].

There is difficulty in diagnosing this entity due to the lack of validated criteria, but it is important to draw attention to the relevance of timely identification of Di-LE and suspension of the culprit drug, which may allow disease remission. With a low awareness of this condition, the aim of this review is to systematize current knowledge about pathophysiology, clinical, and serological disease manifestations, with an update of associated drugs.

Epidemiology

Di-LE may account for approximately 15% of all LE cases[3]. It occurs mainly between 55 and 60 years of age[7], mostly in females and Caucasians[8], but there are also rare pediatric cases reported in patients under treatment with infliximab, carbamazepine[4], and valproic acid[9].

Pathogenesis of drug-induced LE

The pathogenesis of Di-LE remains poorly understood. The fact that several drugs with distinct chemical structures and different pharmacological actions may be associated with Di-LE contributes to the hypothesis that multiple mechanisms are involved, and, in some cases, they may coexist[2]. Genetic susceptibility, drug biotransformation, and epigenetic dysregulation, with changes in innate and adaptive immune response seem to be involved[4].

Given the usual rapid clinical improvement after drug discontinuation, the autoimmune response in Di-LE can be considered as a transient change in immune response and not a significant affectation of the immune tolerance as in idiopathic LE[2]. The risk of a drug to induce Di-LE increases with the number of changes that it causes in the individual's immunity. Procainamide and hydralazine, two of the drugs most frequently associated with Di-LE, induce changes both in the innate and adaptive immune response[2].

Genetic susceptibility

Genetic susceptibility is evident in Di-LE, but risk factors are different for each drug. Human leukocyte antigens (HLA) DR2, DR3, DR4[2], and HLA-B8[3] have been associated with an increased risk for Di-LE induced by minocycline, terbinafine, and hydralazine[2]. Hereditary complement deficiencies, namely, C4 null allele[2] and selective immunoglobulin A (IgA) deficiency, particularly with concomitant HLA-B8 and DR3

haplotypes, have also been hypothesized as risk factor for Di-LE[10].

The slow acetylation phenotype may be a risk factor as some drugs inducing Di-LE, such as procainamide and hydralazine, are metabolized by acetylation through the enzyme N-acetyltransferase[4] and, therefore, slow acetylators may accumulate more antibody-inducing metabolites[2].

A family history of SLE or Di-LE[11] or a personal history of another connective tissue disease[12] may also be considered a risk factor, as reported for terbinafine[3].

Epigenetic dysregulation and autoreactivity/loss of tolerance

Biotransformed drugs and some of their metabolites are responsible for altering the epigenetic properties of B- and T-cells, leading to the formation of autoreactive cells that can induce Di-LE[4].

Both hydralazine and procainamide inhibit DNA methylation in T-cells by decreasing the activity of DNA methyltransferase-1[4] and hypomethylation of T-cell DNA which can alter gene expression profiles and, consequently, T-cell function[8]. This also results in increased expression of lymphocyte function-associated antigen 1 (LFA-1), leading to increased T-cell reactivity and loss of peripheral tolerance[4], which may also occur in idiopathic SLE[2].

In addition, reactive metabolites of procainamide and hydralazine can interfere with central T-cell tolerance, leading to the production of autoreactive T-cells, with hydralazine leading B-cells to produce anti-histone antibodies (H2A-H2B-DNA)[4].

Drug-induced alterations in innate and adaptive immunity

Drugs and/or their reactive metabolites can activate several pathways within the innate immune response and, therefore, enhance the presentation of self-peptides inducing autoimmunity or they can function as haptens and bind to macromolecules triggering an immune response with activation of autoreactive T and B lymphocytes, for example, by antigen mimicry[4]. Given the time lag between drug exposure and onset of clinical and serological abnormalities, the biotransformation of the drug into reactive metabolites is probably responsible for autoimmunity, rather than the drug itself[1].

Inhibition of the classical complement pathway can also contribute to the pathogenesis of the Di-LE, as in the case of hydralazine, penicillamine, isoniazid, and metabolic products of procainamide[4]. These drugs can inhibit the covalent binding of complement factor C4 (classical pathway), increasing the concentration of circulating immune complexes by decreasing their clearance[4].

Quinidine and procainamide inhibit the removal of apoptotic cells by macrophages which allow a greater number of self-antigens to remain longer in circulation and enhance autoantibody formation[4].

Neutrophil extracellular traps (NETs), formed on neutrophil death/apoptosis and consisting of extrusion of a "network" of nuclear DNA and cytosolic proteins, have an important role in host defense, but increased NET formation (NETosis) and/or decreased NET clearance has been associated with different autoimmune diseases, including Di-LE[2]. NETs function as a source of nuclear material rich in autoantigens and granule proteins that enhance the formation of autoantibodies or autoreactive T-cells[4]. In addition, they can cause direct toxicity in host tissues, especially in blood vessels[2].

Both hydralazine and procainamide promote NETosis, the first by increasing calcium influx and activation of peptidyl arginine-deiminase-4 that mediates chromatin decondensation[13] and the latter by activating the muscarinic receptors of neutrophils[4] and propylthiouracil increases the production and decreases the clearance of NETs[2]. However, other Di-LE-inducing drugs such as minocycline and clozapine do not lead to NET formation[2].

Procainamide oxidation by activated neutrophils produces hydroxylamine (PAHA, a toxic metabolite) that combines with neutrophil myeloperoxidase (MPO) and creates cytotoxicity[4] and hydralazine binds to MPO in intracytoplasmic neutrophil granules enhancing the release of cytotoxic and cell death products[13,14]. This type of MPO-induced cytotoxicity enhanced by drug-causing LE *in vivo* is related to their ability to serve as a substrate for MPO *in vitro*[7].

Type I interferons are involved in antiviral response and in bridging innate and adaptive immunity in normal individuals, but these type I interferons have been recognized as an important pathogenic factor in idiopathic SLE. They can be induced by viral particles or by DNA fragments, exposed namely after cell apoptosis or NETs[15], and a chronic type I IFN production with a strong "type I IFN signature", particularly in the skin, has emerged as a major marker in SLE and CLE[16].

Reinforcing the role of type I interferons, there are reports of Di-LE in patients on treatment with IFN-α and IFN-α, but specially with IFN-α, estimated to occur in

0.15-0.7%[17-19]. These cases differ from Di-LE caused by other drugs as they lead to a higher frequency of anti-DNA antibodies (50%) and frequently have cutaneous involvement, also reinforcing the high involvement of type I IFN in CLE[16].

Pathogenesis of Di-CLE

As for SLE, pathomechanisms involved in cutaneous disease are also multifactorial, but it is still uncertain whether similar pathways are responsible for cutaneous disease. The exception is the formation of NETs that are known to be involved in both conditions[20], and very probably inducing type I interferon, whose expression in the skin is one of the highest among all organs involved in idiopathic LE[15,16].

In some individuals, photosensitive drugs such as hydrochlorothiazide, terbinafine, and etanercept can trigger cutaneous LE in photoexposed areas[7], particularly in patients who had already LE serological markers before drug exposure[21]. Apart from keratinocyte necrosis/apoptosis, photosensitive drugs increase Ro/SSA expression on the surface of keratinocytes, as in idiopathic subacute CLE, with consequent increased production of anti-Ro/SSA antibodies and cytotoxicity against these keratinocytes that express the Ro antigen on their surface[22].

Chemotherapeutic agents may induce CLE through cell apoptosis, with release of nucleosides that will act as target for autoantigens and Type I -IFN production[12].

Clinical manifestations of drug-induced LE

The time from starting the drug to the onset of lupus manifestations varies widely between drugs, but Di-LE usually occurs after months to years of exposure[2]. In the case of oncologic therapy, symptoms can occur within days of exposure[7]. The latency period may also be shorter (days or weeks) when the drug is reintroduced[23].

Compared to the idiopathic SLE, Guicciardi et al. reported that patients with Di-SLE are considerably older and have more systemic manifestations, which are probably related to the advanced age and use of more medication[24]. Manifestations may affect many organs as in idiopathic SLE, but organ involvement is relatively specific to the offending drug[8].

Constitutional symptoms such as fever, weight loss, anorexia, and fatigue[1] and symptoms such as arthralgia/arthritis, myalgia, and serositis are the most frequent[13]. Cutaneous manifestations are less frequent, contrasting with 70% of skin involvement in idiopathic SLE[25,26]. An exception is cases induced by anti-TNFα drugs where the skin is involved in > 80% of cases[2]. Occasionally, *sicca* syndrome and Raynaud's phenomenon can also be found[2].

Central nervous system, renal, gastrointestinal, and hematological manifestations are rare[3] and also less frequent than in idiopathic SLE[2], except for neurological involvement for quinidine (up to 30%)[27] and lupus nephritis-like syndromes induced by hydralazine[28-30], sulfasalazine, penicillamine, anti-TNFα, propylthiouracil, apixaban[31,32], and also to phytotherapeutic agents[33] and anti-neutrophil cytoplasmic antibodies (ANCAs) vasculitis associated with hydralazine[30].

Di-CLE

Skin lesions in Di-CLE may present in an unspecified form or with the pattern of subacute or chronic CLE[2]. Subacute CLE is the most common, accounting for 70-80% of cases[7] and occurs mostly in older women often associated with photosensitivity[7].

Cutaneous features are very similar to the idiopathic subacute CLE[24]: erythematous, annular, papulosquamous lesions that do not usually evolve to scarring[7] (Figs. 1 and 2), mainly on photoexposed areas, or occasionally in more protected areas[34]. An atypical and more widespread lesion distribution[35], concomitant bullous and target lesions, vasculitis/purpura[22], and erythema nodosum[26] should raise the suspicion of a drug-induced case, as well as a change in the phenotype of the disease[5].

Chronic CLE is very rarely drug-induced[7], corresponding to the least frequent subtype of Di-LE[34]. It occurs mostly in women, around the age of 40 years[36], more often associated with 5-fluorouracil or anti-TNFα[7], tends to have a slower onset (months to years) and resolves over months[34]. Lesions tend to occur more in photoexposed areas[34] and are clinically similar to the idiopathic form[7] (Fig. 3).

Drug-induced lupus *tumidus* and *chilblain lupus* have also been described[2].

Histological characteristics

Differences between the histology of the idiopathic form of CLE and the drug-induced form have already been suggested, but studies are not concordant. Both forms are associated with focal vacuolization of the

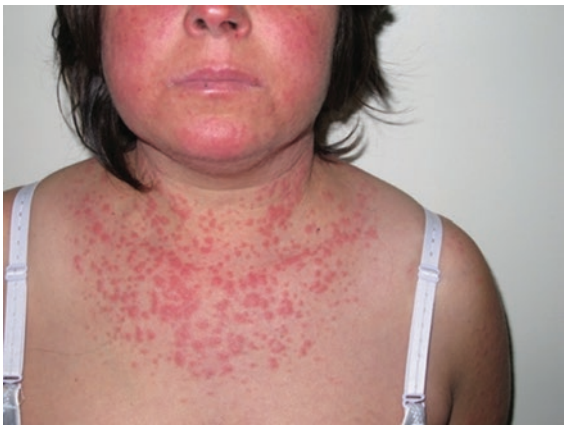

Figure 1. Subacute cutaneous lupus erythematosus induced by isoniazid.

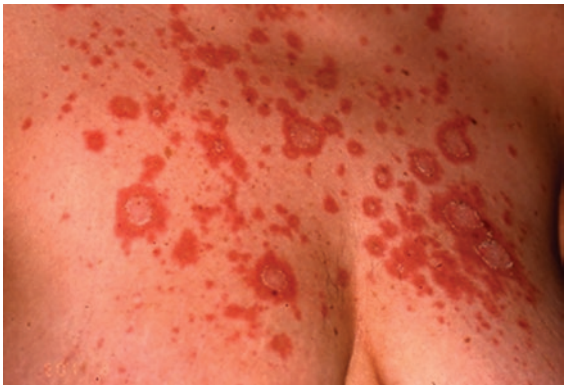

Figure 2. Subacute cutaneous lupus erythematosus induced by terbinafine in a patient with previous history of anti-Ro antibodies.

epidermal basal layer, perivascular and periadnexal lymphocytic infiltrates in the dermis, epidermal atrophy and edema, apoptotic keratinocytes and/or follicular obstruction[22], and both can show granular IgM, IgG and C3 deposits at the dermoepidermal junction[22].

Guicciardi et al. showed that subacute Di-CLE has no significant difference in the average number of eosinophils, basal layer cell liquefaction, keratinocyte necrosis, and depth and pattern of the inflammatory infiltrate but has less mucin deposition, more leukocytoclastic vasculitis, and IgM and C3 deposits in the basement membrane zone are less frequent[24], but for Hillesheim et al., mucin deposition is similar in both forms[37].

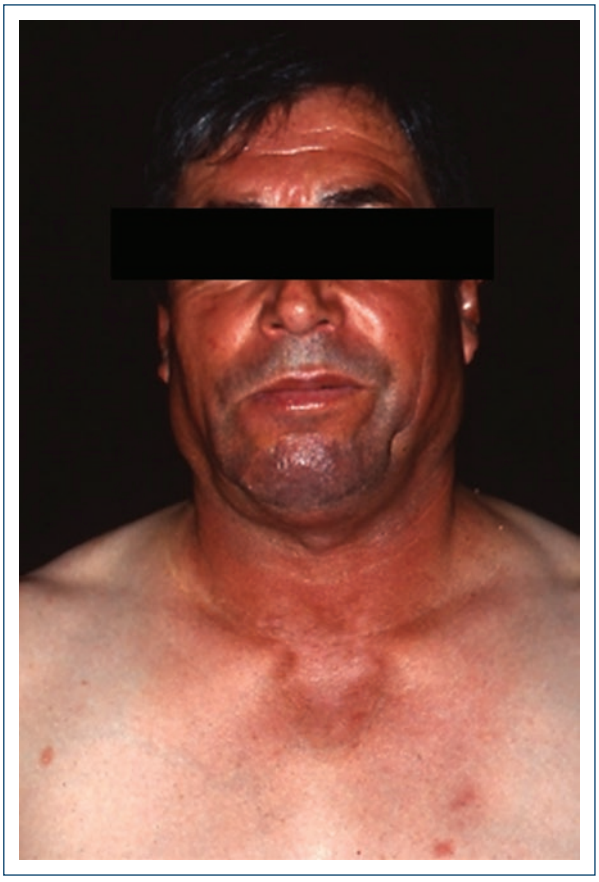

Figure 3. Hydrochlorothiazide-induced chronic cutaneous lupus erythematosus.

Laboratory findings

In Di-SLE erythrocyte, the sedimentation rate is high in up to 80% of patients[8] whereas C-reactive protein tends to be normal, with the exception of quinidine-induced LE (high in 89% of cases)[8]. Anemia, leukopenia or thrombocytopenia are seldom found in Di-LE[1,2], except for thrombocytopenia reported in 47% of quinidine-induced LE[8] and pancytopenia frequently associated with hydralazine[38]. Coombs test is positive in < 30% and low complement levels are rare[1], except in some quinidine-induced forms (low C3 and/or C4 in up to 1/3 of cases)[2].

Autoantibodies to histone subunits, anti-histone antibodies (AHAs) are present in up to 95% of Di-SLE cases[10] and are the hallmark and a very characteristic immunological marker of this form of Di-LE[1], particularly anti-H2A-H2B antibodies in contrast to anti-H3 and H4 histone subunits more frequent in the idiopathic forms[2]. However, this differentiation is not commonly performed and also does not seem to add much

diagnostic value[39]. AHAs can be IgG or IgM, although IgG is more prevalent in Di-LE[38]. Still, their pattern depends on the culprit drug, with procainamide associated with both IgG and IgM and hydralazine and chlorpromazine predominantly IgM[38]. Nevertheless, as AHAs are also present in > 50% of classic SLE, they cannot be used to distinguish drug-induced from idiopathic forms[7]. Furthermore, AHAs are not frequent in the cutaneous forms, and their presence is not synonymous with disease as they develop in 25% of patients treated with isoniazid, but only 1% of these develop clinical manifestations[39].

Antinuclear antibodies (ANAs) are frequent[2]; however, negative ANAs should not exclude the diagnosis, especially if the patient has other LE-associated autoantibodies[23]. Anti-double-stranded deoxyribonucleic acid (anti-dsDNA) antibodies have been identified, mainly in those induced by anti-TNFα agents[1]. Anti-Smith (anti-Sm) antibodies are found in < 5% of Di-LE cases[1], but have recently been described in six cases of Di-SLE[1,32,40-43], one case of subacute Di-CLE[44], and one of chronic Di-CLE[36]. Anti-phospholipid antibodies, such as lupus anticoagulant, have been found in a few cases[13], but, in these cases, the drug may just be unmasking idiopathic SLE as in the case published by Sieiro Santos et al.[45]. Anti-cardiolipin antibody has also been reported in association with hydralazine, procainamide and minocycline[8], metimazole[10,32,45], apixaban[10,32,45], and infliximab[10,32,45].

ANCAs, both anti-proteinase-3 and anti-myeloperoxidase antibodies, have been identified in patients with minocycline and propylthiouracil-induced LE[2], especially in patients with renal and pulmonary vasculitis[14,30,46].

Anti-SSA/Ro (> 90%) and less frequently anti-SSB/La (< 50%) are similarly present in drug-induced and subacute CLE[7], along with positive ANAs in 60-80% of cases[47] by seldom AHAs[48].

High autoantibody titers may persist for months to years after discontinuation of the offending drug, as opposed to clinical manifestations[1].

Diagnosis of Di-LE

Although this entity has been gaining relevance over the years, there is still no consensus about diagnostic criteria[7] and a temporal link with clinical, pathological, and serological findings compatible with LE contributes to establishing the diagnosis[49]. Borchers et al.[8] have proposed the following criteria both for Di-SLE and Di-CLE: - continuous and sufficient exposure to a specific drug, - presence of at least one symptom consistent with LE, - no history of disease before starting treatment, - temporal relationship between the start of the drug and onset of the manifestations, and - discontinuation of the drug and the disappearance of the manifestations[1]. However, this definition still has some flaws, because there are reports of cases that persist despite drug discontinuation[7] and cases of Di-LE in patients with a previous history of SLE[5]. Reappearance of drug reintroducing would contribute to the diagnosis, but this is not recommended[39].

Diagnosing Di-LE can be more difficult for larger latency periods, simultaneous introduction of several drugs, new therapies with little information about their long-term effects[4], and for treatment of neoplastic or autoimmune diseases, as these underlying conditions may be confounding factors[49]. In cases with several potentially suspected drugs, a probability algorithm such as Naranjo's can be used to guide which drug should be stopped first[7].

Drugs frequently implicated in Di-LE

Over the years, an increasing number of drugs have been associated with Di-LE[2], particularly in recent years both due to new therapies used in oncology and autoimmune diseases[2] and due to new associations of "old" drugs[7] (Table 1).

Drugs can be classified as high or low risk[1] or as high, medium, low, and very low risk of inducing SLE[2] (Table 2) or into definitely (isoniazid, procainamide, and hydralazine), probably (phenytoin and carbamazepine), possibly (lithium and lamotrigine) and recently reported to induce Di-LE[4,50]. However, for instance, proton-pump inhibitors (PPIs) and terbinafine[51] are not categorized.

Anti-TNF α-induced LE

LE induced by tumor necrosis factor-alpha inhibitors (anti-TNF α) is rare (< 1%), it affects mostly women[45,52], and in many cases, the drug just reveals a pre-existing LE[2]. It is considered distinct, as it sets up several exceptions to the typical features of Di-LE, but the three main forms of LE have been described[36].

This seems to be a class effect but is particularly evident for infliximab[45] and etarnecept[53]. These drugs induce: - apoptosis enhancing formation of autoantibodies against nuclear antigens[8]; - negative regulation on C-reactive protein and TNFα with consequent decrease in the expression of the adhesion molecule CD44 and reduced clearance of apoptotic material[8]; - and increase in type I interferon levels, which influences plasma cell differentiation[51] – "cytokine shift" with suppression of

Table 1. List of drugs more commonly associated with cutaneous lupus erythematosus, divided by subacute, chronic, and other types of CLE

Subacute cutaneous LE	Diuretics, hydrochlorothiazide[7] Diltiazem[2], amlodipine[35] ACE inhibitors[4], beta-blockers[7], phenytoin, carbamazepine lansoprazole, omeprazole, esomeprazole Anticholinergic agents: tiotropium[7] Terbinafine, antiretroviral therapy[4] Anti-TNFα, anti-IL17, anti-IL12/23[7] Anti-PD1 (nivolumab, pembrolizumab)/anti-PDL1 (atezolizumab), anti-CTLA4 (ipilimumab)[7], Immunoglobulins G, leflunomide[7] Mast cell inhibitors (mastinib), anti-CDK (palbociclib)[51] Allopurinol, mitotane, pirfenidone[4] Bupropion, ticlopidine, rosuvastatin, estroprogestatives[7] Paclitaxel, tamoxifen[51], doxorubicin, docetaxel, gencitabine[7], taxanes, pemetrexed, hydroxyurea[34], 5-FU compounds[62], pazopanib, bevacizumab[21] Topical treatments: terbinafine, imiquimod cream[7], topical beta-blocker[63]
Chronic cutaneous LE	Fluorouracil compounds[2], capecitabine, tegafur, and uracil/tegafur[64] Non-steroidal anti-inflammatory drugs[7], Anti-TNFα (infliximab, etanercept, adalimumab, certolizumab pegol and golimumab[7]), Antifungals, intravenous immunoglobulin[65]
Other forms of cutaneous LE	*Lupus tumidus*: ustekinumab, bortezomide[58] *"Chilblain lupus"*: infliximab, adalimumab, etarnecept[58] Rowell syndrome: terbinafine[7]

LE: lupus erythematosus.

T-helper 1 and increase of T-helper 2 cells, with B-cell activation and autoantibody formation[45,54].

In TNFα-induced-LE cutaneous (Fig. 4), renal, cerebral, and hematological involvement is most commonly seen[45,52] as well as other atypical manifestations such as hepatitis, pneumonitis, valvulitis, deep vein thrombosis, neuritis, and myositis have also been reported[52].

ANAs and anti-dsDNA are very common (90% of cases)[55] as well as anti-cardiolipin antibodies (25% of cases),[45] but anti-histone antibodies are usually negative[2]. Anti-dsDNA antibodies are predominantly IgM with less systemic pathogenicity than the IgG antibodies found in idiopathic SLE, and therefore, this anti-TNFα-induced LE is less severe[53]. These autoantibodies are often present without clinically evident disease[2]. Hypocomplementemia is relatively frequent[2].

In milder cases, patients can tolerate substitution to another anti-TNFα[25,54], and some might tolerate treatment continuation, eventually adding immunosuppressive drugs[45].

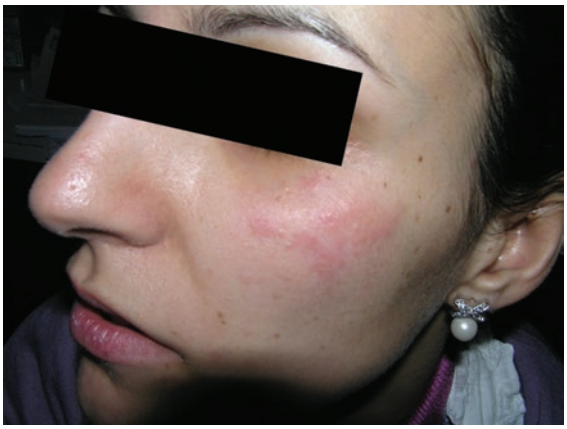

Figure 4. Drug-induced SLE: erythematous asymptomatic lesions on malar areas in a patient who developed ANA after use of anti-TNF-a for Crohn's disease.

COVID-19 vaccine-induced LE

Given the need for rapid development of SARS-CoV-2 vaccines in response to the COVID-19 pandemic, there has not been sufficient time for studies about their adverse effects in the population and, recently, reports of vaccine-associated outbreaks of autoimmune diseases and vaccine-induced cases of LE have been reported[42], as with previous vaccinations[43,56]. Nevertheless, these effects should not discredit vaccination[56].

Patients with autoimmune diseases already have, *ad initium*, a higher propensity to develop complications from the vaccine. It has been reported that 1/3 of patients with idiopathic LE who received SARS-CoV-2 vaccination had an outbreak of their underlying autoimmune disease[43]. Still, in addition to disease exacerbations, Sagy et al. reported the case of three patients with SLE onset after vaccination with the Pfizer BNT162b2 mRNA vaccine, two of whom developed cutaneous manifestations[43]. Khanna et al. reported a case of SLE induced by the Pfizer BNT162b2 mRNA vaccine and reviewed eight other cases induced by the Pfizer, the Astra-Zeneca, and Moderna mRNA vaccines[42]. Most patients were female between 30 and 40 years old, and lupus involved the skin and the musculoskeletal system, followed by the renal and gastrointestinal systems[42].

Possible mechanisms included molecular mimicry and the activation of toll-like receptors (TLRs) on antigen-presenting cells with production of specific autoantibodies[43] or activation of TLRs by the viral mRNA, in conjunction with cytosolic inflammatory components, namely, the pyrin domain of the NLR family (NLRP3), leading to the onset of inflammation and autoimmunity[56].

Table 2. Drugs associated with systemic lupus erythematosus, with organization according to the risk of inducing the systemic type

Very low risk	Statins, anti-TNFα[2] Minocycline[4]
Low risk	Carbamazepine, phenytoin, primidone, ethosuximide[1] Penicillamine, methyldopa, sulfasalazine, minocycline, isoniazid, chlorpromazine, propylthiouracil[2] Captopril, acebutolol[26]
Intermediate risk	Quinidine[2] Isoniazid[4]
High risk	Procainamide (20-30%)[4] Hydralazine (5-10%)[4]

Reversibility and treatment of Di-LE

Clinical manifestations of Di-LE tend to resolve after drug discontinuation, the first recommended therapeutic step (2) that should be associated with lifestyle modifications such as smoking cessation and sun protection[51].

If a lupus-like condition persists after drug withdrawal, treatment should be based on patient's manifestations[2], but this treatment can often be reduced or even discontinued as symptoms resolve[51].

In skin lesions, topical agents, such as corticosteroids or calcineurin inhibitors, are recommended[2] or, when lesions are more generalized, systemic therapies such as anti-malarials, non-steroidal anti-inflammatory drugs (NSAIDs), and corticosteroids may be used[2]. Systemic immunosuppressants such as azathioprine, cyclophosphamide, mycophenolate mofetil[2], or biologic therapeutics[3] may be needed, particularly in Di-SLE with involvement of multiple organs and systems[7].

Reintroduction of the culprit drug may be safe and effective in some cases with minor symptoms, but it is suggested that reintroduction should be associated with a short-term immunosuppressive treatment[57]. Maintenance of treatment with the causative drug has been described in patients under therapy with some anti-TNFα (infliximab and adalimumab), in most cases associated with systemic immunosuppressive agents[58]. This approach can be very useful, especially in patients with chemotherapy-induced LE[34].

For some therapeutic classes, such as PPIs, thiazide diuretics, anti-TNFα, and chemotherapy agents, class effects have been reported[59]; thus, it may be necessary to contraindicate drugs of the same drug class[7]. There are also case reports of the disease recurrence after switching pharmacological classes, which reinforces the idea that there may be some genetic susceptibility for Di-LE[60].

Resolution of clinical manifestations depends on several factors such as the type of drug, the type of clinical manifestations and their severity, and the characteristics of the patients, including their underlying disease[2]. Serological findings take longer resolution[61], so they should not be used for therapy adjustment and evaluation[2]. When the manifestations are not reversible, it might mean that the condition originated from a pre-existing LE that was unmasked by a drug recently added to the patient's medication[2].

Regular follow-up after resolution and in regards to the suspicion of a possible genetic susceptibility for the development of autoimmunity is recommended[13].

Conclusion

Di-LE is indeed gaining importance in current clinical practice and, consequently, the number of studies published on this topic has been increasing, as well as the knowledge about the disease and main culprit drugs. However, most publications are isolated clinical case reports, with few studies adding new information on more precise diagnostic criteria and better knowledge of pathophysiology, characteristics of the implicated drugs, and their risk factors. This might allow, in the future, to screen patients more likely to develop the disease and avoid higher-risk drugs in more susceptible patients. In addition, a greater understanding of Di-LE may also contribute to explain pathomechanisms involved in the idiopathic forms and help develop more targeted treatments.

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Conflicts of interest

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