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REVIEW

Drug-Induced Lupus Erythematosus[☆]

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Abstract Drug-induced lupus erythematosus (DILE) refers to a condition whose clinical, histological, and immunological features are similar to those seen in idiopathic lupus erythematosus but that occurs when certain drugs are taken and resolves after their withdrawal. Over 90 drugs have been linked to DILE to date and the list is growing. Like idiopathic lupus erythematosus, DILE has systemic, subacute cutaneous, and chronic cutaneous forms. A correct diagnosis is very important, as this condition usually resolves after withdrawal of the offending drug.
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Lupus eritematoso inducido por fármacos

Resumen El término lupus eritematoso inducido por fármacos (LEIF) hace referencia a una entidad caracterizada por la aparición de manifestaciones clínicas, histopatológicas e inmunológicas similares a aquellas que aparecen en el lupus eritematoso idiopático, pero que cronológicamente coinciden con la toma de ciertos fármacos y que se resuelven tras la retirada de los mismos. Más de 90 fármacos se han asociado con la aparición de LEIF. Esta lista de fármacos implicados sigue aumentando. Al igual que el lupus eritematoso idiopático, el LEIF se puede subclasificar en lupus eritematoso sistémico inducido por fármacos, lupus eritematoso cutáneo subagudo inducido por fármacos y lupus eritematoso cutáneo crónico inducido por fármacos. Reconocer estas entidades es de gran interés, ya que este cuadro suele revertir tras la retirada del fármaco implicado.
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Introduction

Autoimmune disorders arise from changes in the regulation of one or more components of immune response and involve multiple genetic, epigenetic, and environmental factors that play important roles in triggering and maintaining the process.

Drug-induced autoimmune syndromes have been recognized for some time. The classic example is drug-induced lupus erythematosus (DILE).

Systemic lupus erythematosus (SLE) is an autoimmune disease of unknown origin, but many drugs have been seen to induce lupus-like signs and symptoms. The resulting condition has been referred to variously as DILE, lupus-like syndrome, medicine-induced lupus erythematosus, or drug-related lupus. The condition develops in patients with no history of autoimmune disease and accounts for 10% to 15% of all SLE cases.[2]

The incidence of drug-induced autoimmunity has risen considerably in the last 10 years, and over 90 drugs have been implicated to date. The rapid rise in the number of culprit medications may be attributable to the introduction and use of newly developed drugs in the last 10 years. For example, biologic agents created to block specific phases of the immune response can trigger significant changes in the system. That drugs such as hydralazine, procainamide, isoniazid, quinidine, and chlorpromazine can cause DILE is unquestioned. The highest risk is associated with just 2 drugs: procainamide,[3] which has been linked to DILE in around 20% of treated patients, and hydralazine,[4] which has caused the disorder in 5% to 8% of patients treated at least a year according to standard dosing regimens. On the basis of the low number of cases linked to other drugs, it can be inferred that they seem to involve less risk.

Concept

Although diagnostic criteria are not well established for systemic DILE, it is widely defined as a disorder that resembles SLE but develops when a drug is being taken continuously for at least a month and that disappears when treatment is discontinued. Like lupus, DILE generally causes fever, musculoskeletal pain, and serositis. This clinical picture is usually accompanied by characteristic laboratory findings, specifically serum positivity for antinuclear antibodies (ANA) and antihistone antibodies (AHA). Idiopathic SLE can be difficult to distinguish from systemic DILE given that these 2 entities have similar clinical, serologic and histologic findings. The presence of certain serum markers, and especially resolution of symptoms when treatment with the culprit drug is discontinued, assist in establishing the correct diagnosis.

Epidemiology

The incidence of DILE in the United States has been estimated to be somewhere between 15 000 and 30 000 new cases every year, meaning that the number of patients with this form may be about 10% to 15% of the number with idiopathic SLE.[1] Whereas women with idiopathic SLE outnumber men, systemic DILE affects men and women in similar proportions.[5] Patients with systemic DILE also tend to be older, as patients of advanced age are often prescribed more medications. The prevalence has also been shown to be 6-fold higher in white patients than in black patients.[6] To date, the drug most often associated with systemic DILE is procainamide.

Etiologic and Pathogenic Mechanisms

The etiology and pathogenesis of DILE remains to be fully elucidated, but this disorder probably arises from a combination of features specific to the culprit drug itself and others that are patient-related.

DILE differs from drug hypersensitivity reactions in several ways. First, no evidence of drug-specific T cells or antibodies has been found, nor have target autoantigens directly affected by the culprit drug been detected. Second, DILE develops in relation to the cumulative dose taken and it can take months or even years for symptoms to appear. Finally, symptoms generally take a day or 2 to reappear after rechallenge, indicating the absence of a specific hypersensitivity immune response. It is believed that the development of DILE requires a certain degree of genetic susceptibility, given that patients with relatives who have SLE are more likely to develop the drug-induced form. An individual's acetylator status, which is determined genetically, is also known to play a role.[7] Slow acetylators are homozygous for the recessive gene that controls expression of the liver enzyme acetyltransferase, which is involved in the metabolism of certain implicated drugs, such as procainamide, isoniazid, and hydralazine. Slow acetylators treated with hydralazine or procainamide have also been reported to develop ANA positivity more quickly than fast acetylators and to progress to symptomatic DILE more often. The genetic susceptibility hypothesis recently gained ground after association with certain major histocompatibility complex (HLA) phenotypes. Certain HLA haplotypes—HLA-DR2, HLA-DR4, and HLA-DR3—as well as a slow acetylator phenotype and an unexpressed or ''null'' allele for C4 may be linked to the development of autoimmunity.[8] It is also thought that certain events must occur in sequence before DILE develops.[9] The drug must first undergo biotransformation to a pharmacologically reactive form. The resulting metabolites would have the ability to form stable complexes with self-macromolecules or to directly stimulate lymphocytes, initiating changes that significantly affect the immune system. In this process, activated neutrophils in the bloodstream have been shown to take part in the oxidative metabolism of many drugs implicated in DILE, facilitating the formation of metabolites that trigger autoimmunity[10]; drugs biotransformed in this way include procainamide, hydralazine, quinidine, phenytoin, sulfone, propylthiouracil, penicillamine, chlorpromazine, isoniazid, and carbamazepine. A strong correlation between a drug's susceptibility to myeloperoxidase-mediated oxidative transformation and the tendency of the drug to induce lupus erythematosus has been demonstrated.[10]

The formation of reactive metabolites with similar characteristics could explain why chemically and pharmacologically different drugs are able to induce similar clinical manifestations and trigger autoimmunity.

After these biotransformations, autoimmunity can then be triggered by either the drug itself or its metabolites. Various theories to explain this process have been put forth. One hypothesis postulates that drugs can cause DILE by altering T-cell cell DNA methylation,[11] which has a primordial role in the regulation and expression of genes and cell differentiation. Drugs like procainamide and hydralazine