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Drug-induced systemic lupus erythematosus: A comprehensive review

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Abstract

Drug-induced systemic lupus erythematosus (DILE) is a rare autoimmune disorder that mimics idiopathic systemic lupus erythematosus (SLE), but with a clear temporal relationship to the use of certain medications. This comprehensive review explores the mechanisms, diagnosis, and management of DILE. The condition is primarily immunologically mediated, with drugs triggering immune responses through processes such as antibody formation, T-cell activation, and oxidative stress. Genetic predispositions, including variations in drug-metabolizing enzymes, play a role in susceptibility. Drugs such as hydralazine, procainamide, and minocycline are commonly implicated in DILE, each triggering the formation of autoantibodies, particularly anti-histone antibodies. Diagnosis relies on clinical history, serological testing, and the identification of specific autoantibodies. DILE shares many clinical features with idiopathic lupus but is distinguishable by its typically milder course and absence of renal or neurological involvement. Management primarily involves discontinuing the offending drug, with symptomatic treatment using NSAIDs or corticosteroids. The prognosis is generally favorable, with most symptoms resolving after drug cessation and minimal long-term organ damage. Early recognition and intervention are essential to ensuring a positive outcome and preventing unnecessary treatments.

Keywords: Drug-Induced Lupus Erythematosus; Autoimmune Disorders; Diagnosis of DILE; Anti-Histone Antibodies; Treatment of Drug-Induced Lupus

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder that affects multiple organs and is characterized by the production of autoantibodies. While the majority of SLE cases are idiopathic, a subset of SLE cases is triggered by drugs, known as drug-induced lupus erythematosus (DILE). Drug-induced SLE is a condition where the clinical presentation mimics idiopathic SLE, but it resolves after the discontinuation of the offending drug. Drug-induced lupus is a rare phenomenon, but it is clinically significant because it can lead to misdiagnosis or unnecessary treatment if not recognized correctly [1]. It is estimated that drug-induced lupus occurs in approximately 10-15% of patients with lupus-like symptoms triggered by medications. This means that while lupus-like symptoms may develop in some individuals taking certain drugs, most individuals on these medications do not develop DILE [2, 3]. The incidence of DILE can vary based on demographic factors like age, sex, and underlying health conditions. It is more common in women, especially those aged 40-60 years [4]. Additionally, it tends to develop more often in individuals who already have a genetic predisposition to autoimmune diseases, including systemic lupus erythematosus [5, 3]. Drugs that induce SLE can trigger a variety of immune responses that overlap with idiopathic SLE, making diagnosis and treatment challenging. The mechanisms involved are complex and are still being elucidated [6] This review aims to explore the mechanisms, diagnosis and management of drug-induced SLE.

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2. Mechanisms of Drug-Induced SLE

2.1. Immune System Activation

Drug-induced SLE is primarily an immunologically mediated condition. Certain drugs can alter immune homeostasis, leading to the development of autoimmunity. This process can occur through several mechanisms [7]

2.1.1. Antibody Formation

- Some drugs are metabolized into reactive intermediates that can alter cellular and immune responses. For instance, drugs like hydralazine and procainamide can induce the formation of antinuclear antibodies (ANA), including anti-histone antibodies. These antibodies are a hallmark of drug-induced lupus and play a significant role in triggering the immune response [8]. These altered molecules may be recognized as foreign, leading to immune activation.
- B-cell Activation: Drugs can directly activate B-cells. B-cells are central to the development of autoimmunity, and drug-induced SLE can lead to B-cell hyperactivity. Drugs that induce SLE can promote the production of autoantibodies against nuclear components like DNA and histones. This is particularly evident with drugs such as isoniazid, which can stimulate B-cells to produce these autoantibodies [9].

2.1.2. T-cell Activation

Drugs can also alter T-cell functions. T cells are critical in recognizing and responding to foreign antigens, and in drug-induced lupus, they may become activated due to altered antigen processing or the presence of novel drug-antigen complexes [10]. This leads to a cascade of immune events that can result in systemic inflammation and tissue damage, similar to what is seen in idiopathic SLE [7].

2.2. Drug Metabolism and Toxicity

The metabolism of drugs plays a critical role in the development of drug-induced SLE. Certain drugs are metabolized into toxic intermediates that can alter immune function. For example, drugs like hydralazine and procainamide undergo biotransformation by cytochrome P450 enzymes. The metabolites can form covalent adducts with host proteins, which can then be recognized as foreign by the immune system, inducing an autoimmune response [8].

Genetic Factors: Genetic predispositions also influence an individual's susceptibility to developing drug-induced SLE. Specific polymorphisms in drug-metabolizing enzymes such as N-acetyltransferase (NAT2) and genetic variations in HLA genes have been implicated in the pathogenesis of drug-induced lupus [11]. For instance, slow acetylators of procainamide are more likely to develop lupus-like symptoms, suggesting that genetic variability in drug metabolism is a crucial factor. Also specific polymorphisms in N-acetyltransferase have been shown to influence how hydralazine is processed in the body. Slow acetylators of hydralazine are more likely to develop lupus-like symptoms, suggesting that individuals with this genetic variant are at greater risk of developing drug-induced lupus [11].

2.3. Oxidative Stress and Inflammation

Minocycline has been reported to cause oxidative stress, a condition where there is an imbalance between the production of reactive oxygen species (ROS) and the body's ability to neutralize them. Oxidative stress can trigger inflammatory pathways, leading to immune activation and the subsequent development of lupus-like symptoms [12]. ROS are known to contribute to immune cell activation and tissue damage, which are central to the pathogenesis of lupus [13].

2.4. Molecular Pathways in Drug-Induced SLE

Recent studies have highlighted several molecular pathways that play a critical role in drug-induced lupus.

- **Type I Interferon Pathway:** Type I interferons (IFN-α and IFN-β) are key players in the pathogenesis of autoimmune diseases. Drugs that trigger lupus symptoms can activate the type I interferon pathway, which leads to increased expression of inflammatory cytokines and chemokines that promote autoimmunity [10]. This pathway is particularly important in the induction of systemic inflammation and tissue damage in drug-induced SLE.
- **Neutrophil and Macrophage Dysfunction:** Drugs can also cause dysfunction in neutrophils and macrophages, leading to an exaggerated inflammatory response. This dysfunction can result in the excessive production of reactive oxygen species (ROS), which can cause tissue damage and amplify the autoimmune response [11].

- **DNA Release and Autoantibody Formation:** The interaction between drugs and DNA is central to the development of autoantibodies. Drugs like procainamide and hydralazine may form complexes with histones or DNA, which are then recognized by the immune system. The production of autoantibodies, particularly anti-DNA antibodies, is a hallmark feature of SLE [10].

2.4.1. Specific Drugs and Their Role in Drug-Induced SLE

Several drugs have been implicated in triggering drug-induced lupus, with distinct mechanisms of action:

- **Hydralazine**: This antihypertensive drug is one of the most common drugs associated with DILE. The hallmark of hydralazine-induced lupus is the presence of anti-histone antibodies. These antibodies are directed against histones, proteins involved in the packaging of DNA. In drug-induced lupus, hydralazine's metabolites can form conjugates with histones, leading to their recognition by the immune system as an antigen. The production of these antibodies contributes to the inflammatory processes seen in lupus [14].
- **Procainamide**: Another drug commonly associated with DILE is procainamide, an antiarrhythmic medication. Like hydralazine, procainamide can induce the production of anti-histone antibodies. The mechanism is similar in that procainamide forms immunogenic metabolites that are recognized by the immune system, triggering an autoimmune response [15].
- Other Drugs: Other drugs implicated in drug-induced lupus include quinidine, isoniazid, minocycline, chlorpromazine, and quinidine. These all share the common mechanism of autoantibody formation [16].

3. Diagnosis of Drug-Induced SLE

- Diagnosing drug-induced lupus can be challenging due to the overlap in clinical features with idiopathic SLE. The key diagnostic feature of drug-induced lupus is the identification of specific autoantibodies, particularly anti-histone antibodies, which are typically absent in idiopathic SLE. Serological tests are essential in differentiating between the two conditions, with drug-induced lupus typically showing a negative result for anti-dsDNA and anti-Sm antibodies [14].
- Clinical history is also crucial in identifying drug-induced lupus, including the timeline of drug exposure and symptom onset. A thorough review of the patient's medications can often provide a clue to the diagnosis.
- Clinical Picture of Drug-Induced Lupus
- DILE shares many features with systemic lupus erythematosus (SLE), however, the presentation of DILE is typically milder, and it is often reversible upon discontinuation of the offending drug.

The clinical manifestations of DILE can vary widely but typically include

3.1. Musculoskeletal Symptoms

- Arthralgia (Joint Pain): Joint pain is the most common musculoskeletal complaint in DILE and occurs in approximately 50-75% of cases. The pain can affect multiple joints, often including the wrists, knees, and fingers. Unlike idiopathic SLE, which may cause joint deformities, joint symptoms in DILE are usually non-deforming and transient.
- Arthritis: Some patients may develop inflammatory arthritis, which can cause swelling and stiffness, although it tends to be less severe than in idiopathic lupus.

3.2. Skin Involvement

- Rashes: A malar rash (butterfly-shaped rash across the cheeks and nose) is seen in some cases of DILE, though it is less frequent than in SLE. Photosensitivity (skin rashes triggered by sun exposure) is also a common feature.

3.3. Serositis

- Pleuritis: Inflammation of the pleura (the lining around the lungs) can cause chest pain that worsens with deep breathing.
- Pericarditis: Inflammation of the pericardium (the lining around the heart) can cause chest pain, particularly in the retrosternal region. This is less common than pleuritis in DILE but still occurs in a subset of patients.

3.4. Systemic Symptoms

- Fever: A mild to moderate fever may accompany other systemic manifestations such as fatigue, malaise, and weight loss.
- Fatigue: Patients with DILE often report general fatigue, which can be significant and disabling.

3.5. Renal Involvement

- Proteinuria: Mild to moderate proteinuria (protein in the urine) can occur in some cases of DILE, but renal involvement is much less common and typically less severe than in SLE.
- Hematuria: The presence of blood in the urine may also occur, although gross hematuria (visible blood in the urine) is rare.

3.6. Neurological Symptoms

- Headaches: Although less common in DILE, headaches may occur.
- Cognitive changes: Some patients report symptoms of cognitive dysfunction, which can be similar to those seen in SLE, such as difficulty concentrating or memory problems.
- Seizures and psychosis: These are rarely seen in DILE but can occur in severe cases, particularly if the drug-induced lupus overlaps with other conditions.

3.7. Hematologic Features

- Leukopenia: A decrease in white blood cells can be seen, particularly in the context of drug-induced lupus, but it is generally mild compared to the cytopenia observed in idiopathic lupus.
- Thrombocytopenia: Low platelet count may occur in some patients, though it is less common.
- Anemia: Mild anemia may be seen, though it is typically not severe in DILE.

3.7.1. Distinguishing Features of Drug-Induced Lupus

While DILE shares many features with idiopathic lupus, there are key characteristics that differentiate the two conditions:

3.7.2. Temporal Relationship to Drug Use

Symptoms of DILE usually begin after a prolonged period of drug use (typically 1 to 6 months) but can sometimes develop earlier or after years of treatment. The onset of symptoms is often gradual, and symptoms may improve or resolve rapidly after discontinuation of the offending drug. This temporal association with drug use is a critical differentiating feature of DILE compared to idiopathic lupus, where symptoms often arise without a clear temporal relationship to a specific trigger. Studies have shown that a variety of drugs are implicated in the onset of DILE, with the condition typically emerging several months after initiating treatment [17, 18].

3.7.3. Absence of Renal and Neurological Involvement

In contrast to idiopathic lupus, renal involvement (e.g., lupus nephritis) and neuropsychiatric symptoms (such as seizures or severe cognitive dysfunction) are rare in DILE. This is one of the distinguishing factors, as these features are common in idiopathic lupus, where multi-organ involvement is more prevalent. DILE patients typically do not exhibit the same degree of renal or neurological complications seen in idiopathic lupus, as studies highlight the absence of these manifestations in the majority of DILE cases [19, 20].

3.7.4. Antibodies

Anti-histone antibodies are highly suggestive of DILE, and their presence can help confirm the diagnosis. While anti-nuclear antibodies (ANA) are typically present in both DILE and SLE, anti-histone antibodies are more specific for drug-induced lupus. Patients with DILE usually have a positive ANA and anti-histone antibody profile, whereas those with idiopathic lupus often have other autoantibodies (e.g., anti-dsDNA, anti-Sm).

4. Management of Drug-Induced Lupus

Management of DILE is centered on the discontinuation of the offending drug. In most cases, symptoms improve within weeks to months after the drug is stopped. Additional management steps may include:

- NSAIDs: Nonsteroidal anti-inflammatory drugs are often used to relieve musculoskeletal pain, joint stiffness, and fever [21].
- Corticosteroids: In cases with more severe symptoms (such as significant inflammation or serositis), low-dose corticosteroids may be prescribed to control symptoms [22].
- Hydroxychloroquine: In rare cases, hydroxychloroquine may be considered to help manage the autoimmune response and prevent flare-ups [23].

4.1. Prognosis

The prognosis of drug-induced lupus is generally excellent, with most patients experiencing complete resolution of symptoms after stopping the causative drug. Unlike idiopathic lupus, DILE does not typically cause long-term damage to organs such as the kidneys, heart, or lungs. Renal and neurological involvement is rare in DILE, and those who experience these complications typically have a better prognosis than in idiopathic SLE.

5. Conclusion

Drug-induced lupus erythematosus is a rare but important condition to recognize in patients on long-term medication regimens. It presents with a clinical picture similar to systemic lupus erythematosus but is typically milder and resolves with discontinuation of the offending drug. Early diagnosis and prompt removal of the drug are critical to preventing complications and ensuring a favorable outcome. By understanding the characteristic clinical features, temporal relationship with drug use, and specific antibody profiles, clinicians can distinguish DILE from idiopathic lupus and other autoimmune diseases.

Compliance with ethical standards

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Disclosure of conflict of interest

The author declare that this work was conducted in the absence of any conflict of interest.

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