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Drug-induced Lupus Erythematosus: When to Suspect and How to Diagnose

Catherine Ivory, MD, PhD, FRCPC

Key Takeaways

1. Drug-induced lupus is rare but can occur after prolonged exposure to medications commonly used in gastroenterology, namely proton pump inhibitors and anti-TNF alpha biologic agents.
2. Autoantibodies (ANA and dsDNA) are commonly observed with the use of anti-TNF alpha biologic agents. However, drug-induced lupus should be suspected in the presence of symptoms, primarily rash or arthritis.
3. Clinical manifestations of drug-induced lupus are milder than those of systemic lupus erythematosus and should resolve with cessation of the offending medication.

Introduction

Drug-induced lupus erythematosus (DILE) represents a lupus-like clinical presentation associated with medication use that, by definition, resolves when the offending drug is discontinued.¹ DILE accounts for approximately 10% of “lupus” cases.² The first reported case of DILE was described by BJ Hoffman in 1945, involving

a lupus-like presentation following treatment with sulfadiazine.³ In the following years, similar presentations were reported of cutaneous rashes from anti-hypertensive and anti-arrhythmic agents, with both procainamide and hydralazine listed as high-risk medications for the development of DILE. Although these two medications are prescribed less frequently today, over 100 other medications have been listed in association with DILE, including

more recent therapies such as anti-tumour necrosis factor (TNF) alpha biologic agents and cancer immunotherapies.⁴

For clinicians, diagnosis can be difficult due to the lack of clear diagnostic criteria, patients exposed to polypharmacy with several potential offending drugs, and some patients with pre-existing autoimmune disease. This review summarizes the current understanding of the clinical presentations of DILE, discusses when the diagnosis should be considered, and examines the clinical and serologic differences between anti-TNF alpha-induced lupus and idiopathic systemic lupus erythematosus.

Classification and Clinical Presentation

There are no standard diagnostic criteria for DILE. In general, patients who develop new lupus-like symptoms should be evaluated for possible DILE.⁵ It is important to consider the following factors that support the diagnosis:

- Any prior history of lupus or DILE before drug initiation
- Substantial exposure to the medication, typically over months to years
- At least one objective clinical finding consistent with lupus (i.e. rash or arthritis)
- Appearance of new autoantibodies, such as anti-nuclear antibodies (ANA) and/or anti-double-stranded DNA (dsDNA)
- Symptoms should improve after discontinuation of the drug

DILE can be grouped into three clinical patterns:

- 1. Drug-induced-Systemic Lupus Erythematosus**—common with biologic agents, can present with fever, arthritis, serositis and rash.
- 2. Drug-induced Subacute Cutaneous Lupus Erythematosus**—most common presentation, with new-onset erythematous inflammatory rash, consistent with lupus on biopsy. Often associated with proton pump inhibitors and hydrochlorothiazide.
- 3. Drug-induced Chronic Cutaneous Lupus Erythematosus**—rare presentation seen in older adults, often associated with fluorouracil agents or non-steroidal anti-inflammatory drugs.

DILE should be suspected particularly if the individual has long-term exposure to a known possible culprit medication particularly with symptoms in the absence of an alternate diagnosis. An up-to-date list of all medications and their start date if possible is essential for identifying culprit agents. Although approximately 100 drugs have been implicated in DILE,⁴ the most commonly prescribed drug categories include: **1)** proton pump inhibitors, which are known to cause drug-induced skin rashes, **2)** anti-hypertensive agents, including beta-blockers, ace inhibitors, calcium channel blockers, thiazide diuretics, and hydralazine, which have been associated with lupus-like rashes and **3)** anti-TNF alpha biologic agents which can cause rash, arthritis, and, less commonly, systemic symptoms. Among the anti-TNF alpha biologic agents, infliximab, etanercept and adalimumab are most frequently associated with DILE.

Rashes are the most common clinical presentation of DILE. Subacute cutaneous lupus-like rashes often occur in a photo-distributed pattern, primarily on the face, neck, and extremities. These lesions may appear as a macular/papular or psoriasiform rash, which could be suitable for skin biopsy. However, skin biopsy findings cannot distinguish between drug-induced and idiopathic lupus⁶ except in cases with a clear presence of eosinophilic infiltrates. Rarely, DILE may present with lower-extremity purpura or erythema nodosum. In such cases, further investigation is warranted to rule out infection or vasculitis.

Arthritis is the next most common symptom of DILE, typically presenting with features including pain, swelling, and stiffness of the affected joints. While idiopathic lupus arthritis typically involves the small joints of the hands, DILE can involve small and large joints but typically is not associated with inflammatory back pain or discitis. Pain in general and myalgias are common with DILE and are reported in up to 90% of patients, which can account for symptoms of back discomfort and arthralgias without evidence of specific swelling.⁷ Generally internal organ involvement is extremely rare in DILE. Serositis has been reported in cases of anti-TNF-alpha induced lupus; however, its presence should prompt an extensive work up to exclude infectious causes, particularly underlying autoimmune diseases, such as inflammatory bowel disease or rheumatoid arthritis.⁸

	Systemic Lupus Erythematosus (idiopathic)	Drug-Induced Lupus Erythematosus	Anti-TNF alpha Induced Lupus
Male: Female	1:9	1–2:1	1:1
Age	18–45	>45	>45
Serology	ANA Anti-histone (20–30%) dsDNA (IgG) Anti-Smith Anti-SSA/RO (30–40%) Low C3/C4	ANA (anti-histone 75–95%) Anti-SSA/RO (5%) Normal C3/C4	ANA (anti-histone<50%) dsDNA (IgM) Low C3/C4 Anti-SSA/RO
Manifestations (common)	Malar rash Photosensitivity Alopecia Mucosal ulcers Arthritis Serositis Nephritis Cytopenia Fever/lymphadenopathy	Rash Arthralgia or arthritis Fever Myalgia	Rash Serositis Arthritis Fever

Table 1. Distinguishing Features of Systemic Lupus Erythematosus, Drug-Induced Lupus Erythematosus, and Anti-TNF-Alpha-Induced Lupus; *courtesy of Catherine Ivory, MD, PhD, FRCPC.*

Abbreviations: ANA: anti-nuclear antibodies; dsDNA: anti-double-stranded DNA antibodies; IgG: immunoglobulin G; SSA: Sjögren's Syndrome-related Antigen A

Comparison of Systemic Lupus Erythematosus, Drug-Induced Lupus Erythematosus and Anti-TNF-alpha-Induced Lupus

Although idiopathic systemic lupus erythematosus (SLE), DILE, and anti-TNF-alpha-induced lupus (ATIL) share many clinical features, several distinctive patterns can help distinguish these entities (**Table 1**).

Clinical presentation

Overall, idiopathic SLE has a female predominance and is most commonly diagnosed during the reproductive years, whereas DILE typically presents later in life. DILE has been reported to have a slight male predominance, likely due to increased cardiovascular comorbidities requiring treatment with medications known to trigger the condition.⁹ ATIL also tends to be diagnosed at an older age than idiopathic SLE, although it may be observed across a broader age range due to the expanding use of these biologic therapies.

DILE most commonly presents with a rash, and at times arthritis and fever. Unlike SLE, there are fewer reports of malar rash, mucosal ulcers, or alopecia. Among patients with ATIL, 80% present with rashes,⁷ and arthritis is reported more frequently than in DILE. Although rare, cases of serositis have also been described in ATIL. Lupus nephritis, central nervous system involvement, and cytopenias are exceedingly rare in DILE,¹⁰ whereas these features are well-recognized in idiopathic SLE. Notably, renal involvement develops in up to 50% of patients with idiopathic SLE.¹¹

Serological evaluation

It is important to recognize that the absence of ANA, anti-histone antibodies, or anti-dsDNA does not exclude the possibility of DILE. Nevertheless, ANA positivity is reported in 90–100% of cases,¹² leading some authors to propose its inclusion as part of the diagnostic criteria. However, the presence of autoantibodies alone does not indicate pathology; therefore, a clear history and clinical examination is necessary to interpret laboratory findings. In idiopathic SLE, patients typically demonstrate several high

titre, high affinity autoantibodies, including ANA and anti-dsDNA antibodies. In contrast, DILE is most characterized by ANA positivity, frequently accompanied by anti-histone antibodies, whereas anti-dsDNA antibodies are uncommon. It should be noted, however, that anti-histone antibodies can also be detected in 20–30% of idiopathic SLE patients.¹³ Anti-dsDNA antibodies are commonly detected in ATIL; however, studies have shown that these antibodies are of the immunoglobulin (Ig)M subtype, exhibit lower affinity, and are not thought to be pathogenic compared to the high affinity IgG anti-dsDNA antibodies reported in SLE.¹⁴ Anti-Sjögren's Syndrome A (SSA/RO) antibodies can be detected across SLE, DILE, and ATIL, although at much lower titres than those observed in SLE. Their presence in each condition has been associated with the development of rashes.¹⁵ Hypocomplementemia is unique to SLE. Although reduced complement levels have been reported in some patients with ATIL, they are not observed with DILE.

Autoantibodies often persist even after the offending drug has been discontinued and clinical symptoms have resolved. As a result, repeat testing is not indicated unless new symptoms emerge. Lower-titre antibodies may decline, become negative, or fluctuate over time, particularly in patients receiving immunosuppressive treatments. Importantly, patients can be reassured that a diagnosis of DILE or ATIL does not result in an increased risk of developing SLE.⁵

Diagnostic Approach

A systematic evaluation of the temporal relationship between drug initiation and symptom onset, the types of symptoms, and the exclusion of alternative diagnoses is key for confirming DILE (Figure 1).

- **Assess Clinical Manifestations:** Evaluate for the presence of arthritis (with ultrasound assessment for synovitis when swelling is not clinically apparent), rash (consider skin biopsy), and other manifestations requiring investigations, such as chest X-ray for pleuritic symptoms, or electrocardiography and echography for suspected pericarditis. Concurrently, alternative diagnoses, including infection and cancer, should be excluded.
- **Evaluate the Timing and Type of Drug Exposure:**
 - Acute symptom onset (7–14 days post new medication) → suggestive of a drug reaction rather than DILE
 - Chronic symptom onset (months to years after drug initiation) → supports consideration of DILE
 - Drug is known to potentially cause DILE
- **Review Serology Findings:**
 - ANA positive and anti-dsDNA positive → may suggest ATIL.
 - ANA positive and anti-histone antibody positive → supports a diagnosis of DILE
- **Discontinue Offending Drug:**
 - **Treat symptoms of DILE or ATIL:** NSAIDs for arthritis, topical steroids for rashes, and corticosteroids for more severe presentations (serositis)
- **Assess for Resolution:**
 - DILE → symptoms typically resolve within weeks
 - ATIL → symptoms typically resolve within 2–3 months, although recovery time can vary depending on the patient and the type of causative medication
- **Consider Alternate Therapy:** if ongoing treatment remains indicated

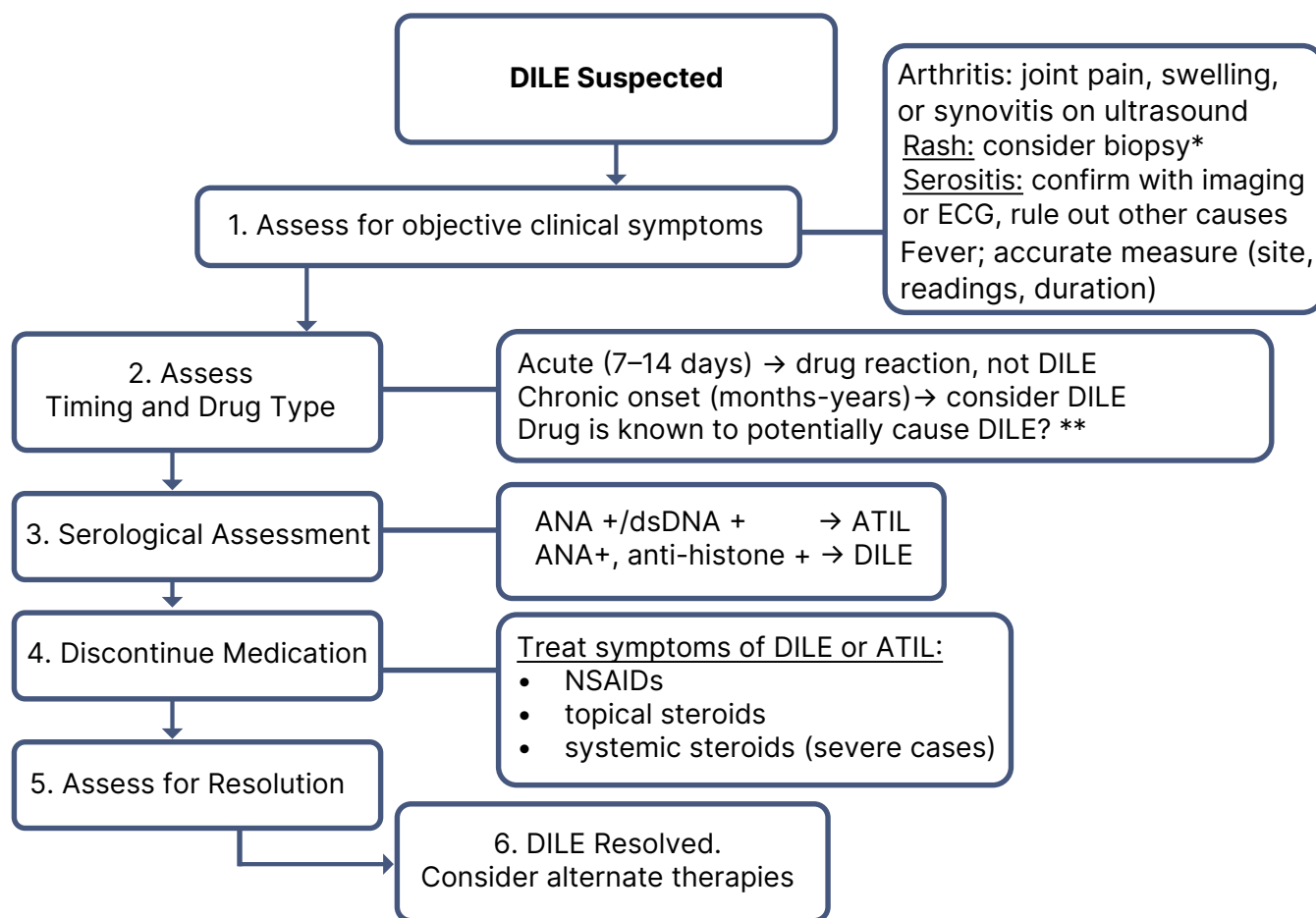


Figure 1. Approach to Drug-Induced Lupus Erythematosus (DILE); courtesy of Catherine Ivory, MD, PhD, FRCPC.

* Skin biopsy of affected lesions should provide histological findings consistent with lupus.

** For a list of drugs known to be associated with DILE.^{4,5}

Abbreviations: ECG: electrocardiogram; ANA: anti-nuclear antibodies; ATIL: anti-tumour necrosis factor- induced lupus; DILE: drug-induced lupus erythematosus; dsDNA: anti-double-stranded DNA antibodies; ATIL: Anti-TNF-induced lupus; NSAIDs: non-steroidal anti-inflammatory drugs.

Other Considerations for ATIL

- Patients with inflammatory bowel disease, rheumatoid arthritis, or spondyloarthropathies may have baseline ANA positivity. ANA positivity was found at baseline in 43.6% of rheumatoid arthritis patients and increased to 73% after infliximab exposure, whereas anti-dsDNA antibodies were only present in 9.5% of patients after treatment.¹⁶ After 6 months of infliximab therapy for various approved indications including inflammatory bowel diseases, ANA was positive in 69.4% of patients but only one patient (1/268) developed ATIL.¹⁷ For this reason, some experts have suggested obtaining baseline reference ANA and anti-dsDNA testing prior to starting anti-TNF alpha therapy.^{18,19}
 - A positive baseline result does not preclude the use of biologic therapy.
 - Developing positive ANA or anti-dsDNA antibodies after initiating anti-TNF therapy is common and, in the absence of clinical symptoms to suggest ATIL, does not predict the development of ATIL or warrant discontinuation of the medication.
 - No further monitoring or testing for ANA or dsDNA is required unless DILE or ATIL is suspected.
- If ATIL is confirmed, switching to a biologic with an alternative mechanism of action is recommended. However, in selected patients for whom anti-TNF alpha therapy remains the best therapeutic option, continued use may be considered in individuals who experience only mild ATIL symptoms, such as limited rash or mild arthritis.
 - Rechallenge with the same medication is discouraged, as it could lead to recurrence of DILE within days to weeks and should only be undertaken with close clinical monitoring.
- Infliximab has been associated with a higher risk of auto-antibody production, likely based on its chimeric antibody structure. Nevertheless, the reported rate of ATIL remains low, occurring in 0.5–1% of users, indicating that it is a rare phenomenon and that anti-TNF alpha therapy remains a safe therapeutic option.¹⁸

Conclusion

DILE remains a clinical diagnosis, as no clear diagnostic criteria exist. However, it should be strongly suspected in patients who develop new-onset rash or arthritis following prolonged drug exposure. ANA positivity, often corresponding to the presence of anti-histone antibodies, is common in DILE, whereas anti-dsDNA antibodies are more frequently observed in ATIL. Exclusion of alternate causes for the symptoms is essential when DILE is suspected. When DILE is correctly identified, symptoms will resolve following discontinuation of the offending medication. Therefore, early identification of DILE is critical to facilitate prompt drug discontinuation and often requires a multidisciplinary approach involving gastroenterology, dermatology, and rheumatology.

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