

# Methimazole Induced Lupus Erythematosus: A Case Report and Literature Review

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## Abstract

Drug-Induced Lupus Erythematosus (DILE) is a rare drug-related reaction characterized by symptoms and laboratory findings similar to those of idiopathic lupus. We describe a case of DILE developed after methimazole administration. In this case, a man with a history of hyperthyroidism received methimazole for approximately two years. One year prior, he presented with a discoid rash, arthralgia, and intermittent fever. Routine laboratory examination revealed an elevated erythrocyte sedimentation rate and C-reactive protein levels, decreased complement levels, and abnormal autoantibodies. Histopathological examination revealed mucin staining, and the lupus band test was negative. The patient was diagnosed with DILE and treated with methylprednisolone and hydroxychloroquine after the immediate discontinuation of methimazole. In conclusion, this case report describes a distinctive discoid cutaneous lesion of methimazole-induced lupus erythematosus that is very rare in clinical practice. We hope that this will improve awareness of this disease in clinical practice.

**Keywords:** Drug-induced lupus erythematosus; Antithyroid drugs; Fever; Rash; Literature review

## Introduction

Drug-Induced Lupus Erythematosus (DILE) is an uncommon drug-induced adverse effect often characterized by a clinical phenotype similar to Systemic Lupus Erythematosus (SLE) [1]. Clinical manifestations are temporally related to continuous drug exposure and resolve upon discontinuation of the drug [2]. Methimazole, an antithyroid drug commonly used to control hyperthyroidism, is associated with several toxic adverse reactions such as agranulocytosis, hepatitis, and liver function damage [3,4]. Antithyroid drugs generally cause rheumatic immune diseases mainly presenting as antineutrophil cytoplasmic antibody-associated vasculitis [5]. However, methimazole-induced lupus syndrome is relatively rare. Here, we report a case of methimazole-induced lupus erythematosus that occurred 2 years after methimazole administration. The patient presented with arthralgia, intermittent fever, and skin symptoms of a discoid rash, which is very rare in clinical practice.

## Case Report

A 68-year-old man presented with a 12-month history of arthralgia, intermittent fever, and a discoid rash. He was diagnosed with hyperthyroidism and received methimazole treatment in January 2020. His medical history indicated that he had Graves' hyperthyroidism. The diagnosis was confirmed by a positive test for thyrotropin receptor autoantibodies and ocular magnetic resonance imaging which indicated thyroid ophthalmopathy. After evaluation, the patient was administered methylprednisolone shock treatment (0.5 g twice daily for 3 days and 0.25 g once a day for 3 days), and the symptoms of Graves' hyperthyroidism were relieved to some extent. Since then, the patient took methylthiamidazole 5 mg once daily to treat hyperthyroidism. Twelve months prior, he had intermittent fever, joint pain, and rashes without obvious inducement. The fever lasted for half a day, and resolved spontaneously. Joint pain involved the wrists, fingers, and neck; joint swelling and redness were also observed. Pain-relieving medications were ineffective, and the patient received

anti-infectious treatment. Blood tests at that time revealed leukopenia. Therefore, methimazole administration was changed to oral propylthiouracil. However, one month of propylthiouracil therapy had a poor effect on his hyperthyroidism. Thus, a methimazole transdermal agent was selected for external use. The patient was admitted to our hospital for diagnosis and treatment. Physical examination revealed a body temperature of 37°C. Multiple circular erythemas with skin pigmentation, such as discoids, were present on his limbs (Figure 1A), trunk, and neck area. In addition to the symptoms mentioned above, the patient reported a weight loss of 10 kg without photosensitivity, alopecia, oral ulcers, and Raynaud's phenomenon.

Laboratory investigations were performed to assess the patient status. Tests for Anticardiolipin Antibody (ACA) and anti-β<sub>2</sub>-glycoprotein 1 were positive; Anti-Nuclear Antibody (ANA) was negative. Meanwhile, the anti-double-stranded DNA (anti-dsDNA) antibody level was 15 IU/mL, also defined as negative. However, in December 2021, ANA was positive at 1:80, with a homogenous pattern. Further identification showed positive anti-dsDNA (201.6 IU/mL) and ACA. The other laboratory tests showed recent onset of mild anemia (Hb 66 g/L), elevated erythrocyte sedimentation rate (>140.0 mm/H), C-reactive protein (134.00 mg/L), and hypoalbuminemia. Of note, complement (C3 and C4) levels were low. Serum protein electrophoresis showed polyclonal hypergammaglobulinemia with an elevated IgG level

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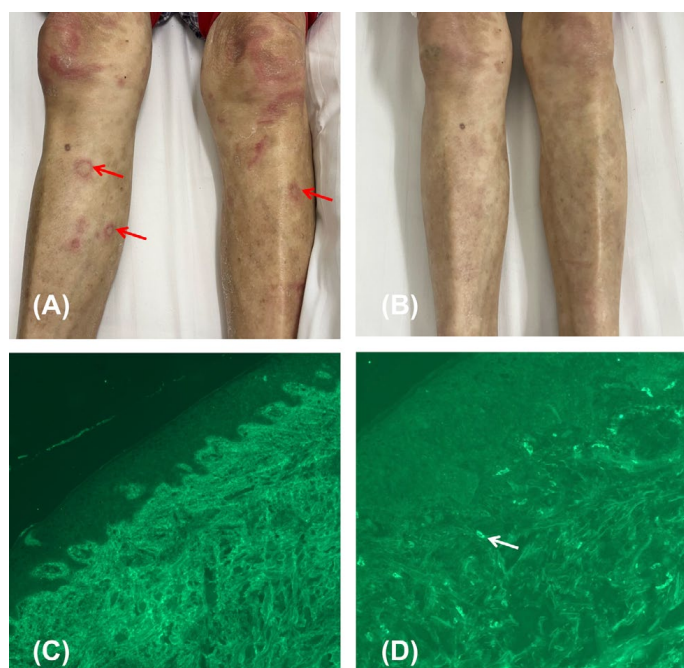
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(23.30 g/dL; reference range 7.51–15.6). Further examination showed elevated serum IgG4 levels. The Coombs test (direct antiglobulin test) was positive, without evidence of hemolysis. To exclude hematologic disorders, bone marrow puncture was performed. Bone marrow cell morphology and flow cytometry analysis indicated no significant abnormalities. Additionally, thyroid function tests revealed that the patient was in a hyperthyroid state. For further diagnosis, a biopsy of erythema multiforme-like lesions on the lower limb was performed. Light microscopy revealed non-specific changes and mucin-negativity. Meanwhile, the results of direct immunofluorescence showed that C1q was positive in superficial dermal blood vessels (Figure 1D), whereas IgA, IgG, IgM, C3, and C4 were negative, indicating that the lupus band test was negative (Figure 1C). Based on the medical history, clinical manifestations, laboratory data, and biopsy results, the patient was

diagnosed with DILE. The medical history of the patient is presented in Supplementary Table 1.

The patient used methimazole for nearly 3 years in oral and external dosage forms, and since it is a potential inducer of DILE, it was immediately discontinued. Furthermore, the patient was administered methylprednisolone (40 mg once daily for 8 days) and hydroxychloroquine. A few days later, the erythema substantially faded with left hyperpigmentation (Figure 1B), and the joint pain was relieved. Meanwhile, the patient’s body temperature returned to normal without recurrence. The laboratory data before and after treatment are shown in Figure 2. The results indicate that after several days of treatment, the erythrocyte sedimentation rate decreased. However, the levels of WBC and RBC still did not recover; this might be due to the short treatment time, and further observation is needed. Subsequent radioactive iodine therapy was recommended for his hyperthyroidism.



**Figure 1:** (A) Skin rash appeared in our patient during therapy with methimazole. (B) Erythema substantially faded with hyperpigmentation left after treatment with methylprednisolone and hydroxychloroquine and discontinuation of methimazole. (C) Direct immunofluorescence of IgA, IgG, IgM, C3 and C4 in lesional skin (100× magnification). (D) Direct immunofluorescence of C1q (100× magnification). The red arrowhead: discoid lesions. The white arrowhead: C1q was positive in superficial dermis blood vessels.

### Discussion

DILE is a lupus-like disease that is caused by drug exposure. Drugs with definite proof of association with DILE include hydralazine, procainamide, isoniazid, methyldopa, and chlorpromazine. DILE diagnosis requires the following features to be present: 1) exposure to a drug suspected to induce DILE; 2) no history of SLE prior to drug therapy; 3) detection of positive ANA with at least one clinical sign of SLE; and 4) rapid improvement and a gradual fall in ANA, and other serologic findings, upon withdrawal of the drug [6]. In our reported case, methimazole is the drug which was suspected to induce DILE. Moreover, our patient had no history of SLE, was ANA-positive, and presented with lupus-like manifestations. After discontinuing methimazole administration, the patient’s symptoms gradually improved. According to the follow-up result, the patient has no discomfort. Therefore, the diagnosis of DILE was considered.

Methimazole is an antithyroid molecule that has moderate potential to elicit DILE. The mechanism by which antithyroid drugs trigger DILE may be associated with drug-mediated changes in the structure of the DNA-histone complex. These changes prevent the histones from being hydrolysed, which causing immunogenicity or expose new epitopes [5,7,8]. A literature review of antithyroid-DILE was conducted by searching PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>) [3,9-15]. Articles on antithyroid-DILE with skin symptoms published from the 1980s till date were selected, and those without full text were excluded. A summary of previous reports which show that antithyroid-DILE with skin manifestations is rare, is listed in Table 1. The results indicated that the skin symptoms included purplish red erythema, vesiculopapules, and bullous formed. We described a case

**Table 1:** Skin symptoms of DILE associated with antithyroid agents.

Authors	Published Year	Number of Cases	Drug	Skin Symptoms
Searls et al. [8]	1981	2	PTU	Violaceous plaques with white border on the palms of hands with body itching
			MMI	diffuse rash
Takuwa et al. [9]	1981	1	PTU/MMI	pruritic macular rash in neck and chest with generalized erythrodermia
Sato-Matsumura et al. [10]	1994	1	PTU/MMI	purplish red erythema on the cervicofacial region, chest, hands and four extremities
Thong et al. [11]	2002	1	MMI	vesicles and crusts on the lower leg, dorsa of the hands and feet
Aloush et al. [12]	2006	1	PTU	vesiculo-papular eruption on hands
Seo et al. [13]	2012	1	MMI	discrete tense bullous lesions and generalized itchy erythematous to brownish polymorphic patches on the back and four extremities
Venturi et al. [14]	2016	1	MMI	an erythematous–oedematous, irregularly oval and translucent patch with scaly crusts on the nasal pyramid
Beernaert et al. [3]	2020	1	MMI	malar rash
Ours case	2022	1	MMI	discoid lesions on the legs and scattered erythema on the back and neck

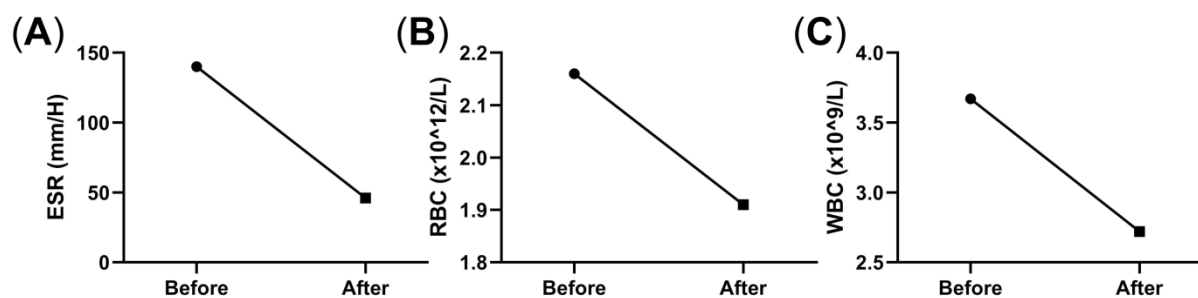


Figure 2: (A) The ESR level before and after treatment. (B) The count of RBC before and after treatment. (C) The count of WBC before and after treatment.

of methimazole-induced lupus erythematosus with discoid erythema lesions, which was significantly different from the other cases.

DILE is characterized by clinical and laboratory findings similar to those of idiopathic lupus; therefore, a differential diagnosis of idiopathic SLE is necessary. First, the patient developed symptoms one year after the use of methimazole. This is consistent with a previous report that DILE develops 2 weeks to 3.2 years after drug use [14]. Second, the rash was distributed over the trunk, particularly in the lower extremities. In idiopathic SLE, rashes usually develop in the sun-exposed upper body [2]. Third, the clinical manifestations of DILE include fever and arthritis, but other common systemic symptoms of SLE, such as renal injury and neurological involvement, are uncommon in DILE.

DILE treatment involves discontinuing the causative drug. Importantly, our case indicates that a methimazole transdermal agent for external use could also induce DILE. Therefore, when patients manifest lupus-like manifestations, even if non-specific, such as joint pain or swelling, cutaneous lesions, systemic manifestations, and ANA positivity, a careful search for drugs that can induce lupus is essential.

## Conclusion

In summary, early diagnosis of DILE and differentiation between DILE and SLE is very important, especially in patients with a history of specific medication. First, immediate cessation of the drug is crucial if DILE is considered. Second, accurate diagnosis in a short time and improved understanding of this disease requires the unique knowledge and experience of clinicians.

## Ethics Statement

This article was performed in accordance with the principles of Declaration of Helsinki. The patient gave written informed consent for the case to be published (including publication of images). Ethical review and approval was not required to publish the case details in accordance with the local legislation and institutional requirements. Since it is a case report with no more than three cases, the report is derived from a review of medical records and cannot be linked to an individual unless the written consent of the patient is obtained.

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