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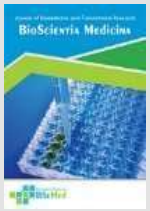

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A Rare Case of Antithyroid Drug-Induced Lupus Erythematosus, Graves' Disease, and Primary Infertility

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A B S T R A C T

Background: Drug-induced lupus erythematosus (DILE) is a rare autoimmune disorder that mimics idiopathic lupus erythematosus, triggered by certain medications. This case report presents a patient with DILE induced by methimazole, a commonly used antithyroid drug, along with Graves' disease and primary infertility. **Case presentation:** A 41-year-old woman presented with palpitations, a history of Graves' disease treated with methimazole, and primary infertility. She developed lupus-like symptoms including fever, joint pain, and skin rash. Examination revealed tachycardia, tenderness of the right and left knee joints and limited range of motion. Laboratory investigations confirmed hyperthyroidism and autoimmune features consistent with DILE. **Conclusion:** This case highlights the rare occurrence of DILE induced by methimazole, emphasizing the importance of recognizing and managing this condition in patients receiving antithyroid drugs.

1. Introduction

Drug-induced lupus erythematosus (DILE) stands as a complex and often perplexing medical phenomenon, a testament to the intricate interplay between the human immune system and the pharmacological agents employed to treat its myriad maladies. Defined as a lupus-like syndrome that arises secondary to exposure to certain medications, DILE mirrors the clinical and immunological features of idiopathic systemic lupus erythematosus (SLE) but typically resolves upon discontinuation of the offending drug. This intriguing condition, first recognized in the 1940s, has garnered increasing attention in recent decades due to the burgeoning development and use of new therapeutic agents. DILE represents a unique challenge for clinicians, as it often mimics SLE, a chronic autoimmune disease characterized by a diverse array of clinical manifestations, including fatigue, joint pain, skin rashes, and renal involvement. The diagnostic process for DILE can be particularly intricate, requiring a high index of suspicion, meticulous evaluation of the

patient's medication history, and careful correlation of clinical and laboratory findings.[1-4]

The prevalence of DILE remains uncertain, with estimates suggesting that it accounts for approximately 10% of all lupus cases. However, the true incidence may be higher, as many cases may go unrecognized or be misdiagnosed as idiopathic SLE. The clinical spectrum of DILE is broad, ranging from mild, self-limiting symptoms to severe, life-threatening complications. The most commonly reported manifestations include arthralgia, myalgia, fever, and serositis. Renal and neurological involvement are less frequent but can occur in some cases. The pathogenesis of DILE is complex and not fully elucidated. However, it is believed to involve a combination of genetic predisposition, environmental factors, and drug-specific mechanisms. The drugs implicated in DILE are diverse, encompassing a wide range of therapeutic classes, including antihypertensives, antiarrhythmics, anticonvulsants, and antimicrobials. The mechanisms by which these drugs trigger DILE are varied and may involve direct activation of the immune system, alteration of self-antigens, or impairment of immune tolerance.[5-8]

The management of DILE centers on the prompt identification and withdrawal of the offending medication. In most cases, this leads to resolution of symptoms and improvement in laboratory abnormalities. However, some patients may require additional treatment with corticosteroids or immunosuppressive agents to control disease activity.[9,10] This case report presents a rare and intriguing case of DILE induced by methimazole, a commonly used antithyroid drug, in a 41-year-old woman with Graves' disease and primary infertility.

2. Case Presentation

Mrs. SA, a 41-year-old woman, presented to the Endocrinology and Metabolism Clinic at Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia, with the chief complaint of worsening palpitations over the preceding week. The palpitations were characterized as a rapid, pounding sensation in her chest, accompanied by a feeling of anxiety and lightheadedness. These episodes were particularly pronounced during periods of physical exertion or emotional stress and had become increasingly frequent and severe, prompting her to seek medical attention. In addition to her primary complaint, Mrs. SA also reported experiencing intermittent joint pain, particularly affecting her knees, for the past three months. The pain was described as a dull, aching sensation, accompanied by stiffness and a limited range of motion. She had also noticed a recent increase in hair loss, exceeding her usual shedding, and occasional episodes of fever, typically low-grade and occurring in the afternoon or evening.

Further inquiry into her medical history revealed a diagnosis of Graves' disease approximately one year prior. Graves' disease is an autoimmune disorder characterized by hyperthyroidism, a condition resulting from excessive production of thyroid hormones. At the time of her initial diagnosis, Mrs. SA had presented with a constellation of symptoms suggestive of hyperthyroidism, including palpitations, heat intolerance, excessive sweating, fatigue, and anxiety. She had been prescribed methimazole, an antithyroid medication that inhibits the synthesis of thyroid hormones. Initially, she responded well to the medication, with a marked improvement in her symptoms. However, three months prior to her current presentation, she began experiencing the aforementioned symptoms of joint pain, hair loss, and fever, raising concerns about a possible adverse drug reaction or an underlying autoimmune condition.

Mrs. SA also reported a history of primary infertility, having never conceived despite being married for 16 years and actively attempting to become pregnant. She had undergone several evaluations and treatments for infertility, but none had been successful. On physical examination, Mrs. SA appeared generally well, alert, and oriented. Her vital signs were as follows: blood pressure 130/90 mmHg, pulse 130 beats per minute, respiratory rate 20 breaths per minute, and temperature 36.7°C. Her body mass index (BMI) was calculated to be 22.9

kg/m², placing her within the healthy weight range.

Examination of her head and neck revealed diffuse hair thinning but no other significant abnormalities. There was no evidence of a malar rash, a butterfly-shaped rash across the cheeks and nose often seen in lupus, nor was there any exophthalmos, a protrusion of the eyeballs commonly associated with Graves' disease. Her thyroid gland was not visibly enlarged. Cardiovascular examination revealed a rapid heart rate, consistent with her complaint of palpitations, but no murmurs or other abnormal heart sounds. Auscultation of her lungs was unremarkable. Examination of her abdomen was also normal. Musculoskeletal examination focused on her knee joints, which were the primary sites of her reported pain. There was no obvious swelling or erythema, but palpation elicited tenderness along the joint lines bilaterally. Range of motion was mildly restricted due to pain and stiffness.

Based on her clinical presentation and preliminary findings, a comprehensive laboratory evaluation was ordered to further assess her condition. This included a complete blood count, a metabolic panel, thyroid function tests, and autoimmune markers. The results of her laboratory investigations were as follows; Complete blood count: Hemoglobin 10.6 mg/dL (slightly low, suggesting mild anemia). Leukocytes 6680/mm³ (within the normal range). Platelets 182,000/mm³ (within the normal range); Metabolic panel: Cholesterol 247 mg/dL (elevated). Triglycerides 614 mg/dL (significantly elevated). HDL-C 35 mg/dL (low). LDL-C 89 mg/dL (within the normal range); Thyroid function tests: Free T4 58.51 pmol/L (elevated, indicating hyperthyroidism). TSHs <0.05 µIU/mL (suppressed, consistent with hyperthyroidism); Autoimmune markers: ANA (IF) >1:1000 (strongly positive, suggesting autoimmune disease). Anti-dsDNA 676.9 (significantly elevated, indicative of lupus). Histone antibody 3.9 (>2.5 strong positive, further supporting lupus).

In addition to the laboratory tests, an echocardiogram was performed to evaluate her cardiac function in light of her palpitations and history of Graves' disease. The echocardiogram revealed an ejection fraction (EF) of 72%, indicating normal heart function, and minimal pericardial effusion, a small accumulation of fluid around the heart. To further assess her symptoms and laboratory findings, Mrs. SA was evaluated by a rheumatologist and an immunologist. The rheumatologist applied the EULAR/ACR classification criteria for systemic lupus erythematosus (SLE), a set of diagnostic criteria used to classify and diagnose lupus. Mrs. SA met several of these criteria, including arthritis, fever, hair loss, and the presence of specific autoantibodies, resulting in a total score of 25. This score, exceeding the threshold of 10, confirmed the diagnosis of SLE.

The immunologist assessed her disease activity using the MEX-SLEDAI score, a tool used to quantify the severity of lupus activity. Her MEX-SLEDAI score was 6, indicating moderate disease activity. Given her diagnosis of SLE and the presence of anti-histone antibodies, which are strongly associated with drug-induced lupus, the possibility of drug-induced lupus erythematosus (DILE) was considered. DILE is a condition that mimics SLE but is triggered by certain medications. In Mrs. SA's case, methimazole, the antithyroid medication she had been taking for Graves' disease, was identified as the likely culprit. In addition to her physical symptoms, Mrs. SA's emotional well-being was also assessed. She completed the Beck Depression Inventory-II (BDI-II), a questionnaire used to screen for depression. Her score of 14 indicated mild depression, likely related to the challenges of coping with her chronic illnesses and infertility. Based on the comprehensive evaluation, including her clinical presentation, laboratory findings, and specialist consultations, a diagnosis of antithyroid drug-induced lupus erythematosus (DILE), Graves' disease, and primary infertility was established. This complex combination of conditions presented a unique therapeutic challenge, requiring careful consideration of the interplay between her autoimmune disorders, medication side effects, and reproductive health.

Table 1. Clinical and laboratory findings.

Category	Findings
Clinical findings	- Palpitations- Intermittent fever- Malar rash (initially present, resolved at the time of examination)- Joint pain, particularly in the knees- Hair loss- No oral ulcers- Fine tremors- Joint tenderness and limited range of motion
Laboratory findings	- Hemoglobin: 10.6 mg/dL- Leukocytes: 6680/mm^3- Platelets: 182,000/mm^3- Cholesterol: 247 mg/dL- Triglycerides: 614 mg/dL- HDL-C: 35 mg/dL- LDL-C: 89 mg/dL- Free T4: 58.51 pmol/L- TSH: <0.05 μIU/mL- ANA (IF): >1:1000- Anti-dsDNA: 676.9- Histone antibody: 3.9 (>2.5 strong positive)
Other investigations	- EULAR/ACR classification criteria score: 25- MEX-SLEDAI score: 6 (moderate disease activity)- BDI-II score: 14 (mild depression)- Echocardiography: EF 72%, minimal pericardial effusion

Table 2. Treatment and follow-up.

Category	Details
Initial treatment (prior to clinic visit)	- Methimazole (discontinued due to suspected DILE)- Treatment for lupus at a private hospital (unspecified)
Treatment at the clinic	- Methylprednisolone 1x8 mg- Mycophenolic Acid 1x360mg- Hydroxychloroquine 1x200mg- $CaCO_3$ 3x500mg- Paracetamol 650mg- PTU 3x100mg- Propanolol 3x10mg- Fenofibrate 1x300mg- Candesartan 1x8mg- Gabapentin 2x 100 mg- Cendo Lyters ED 6x1tts ODS- Merlopam 1x0.5mg- Fluoxcetine 1x10mg
Follow-up	- 3 months after initial treatment, lupus activity decreased (MEX-SLEDAI score of 2)- Graves' disease was better controlled

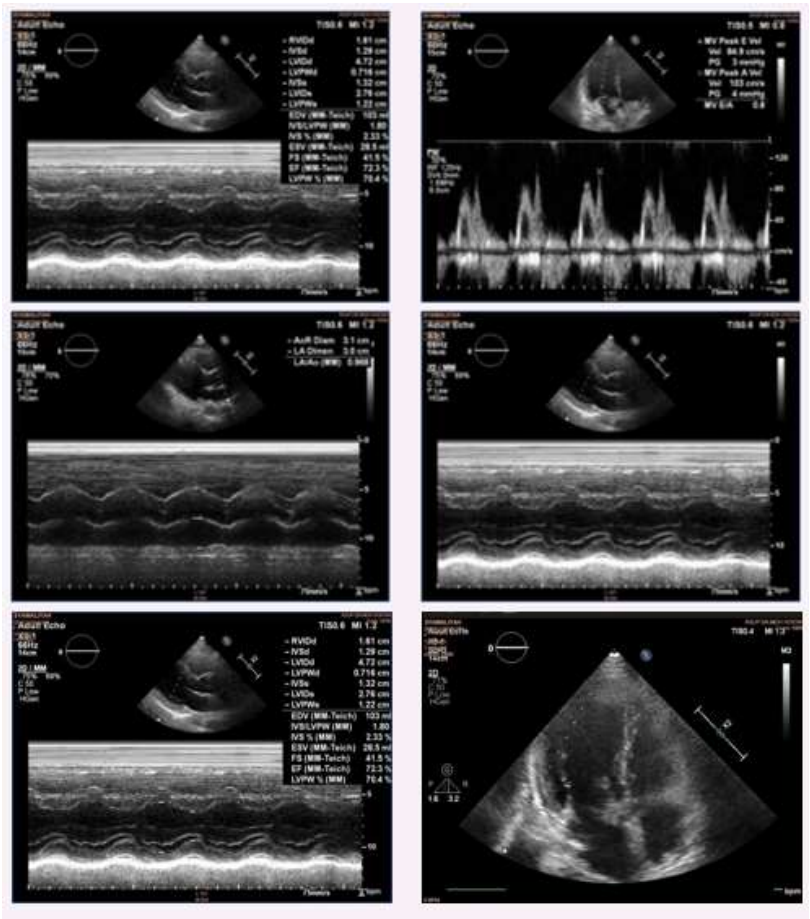

Figure 1. Echocardiography.

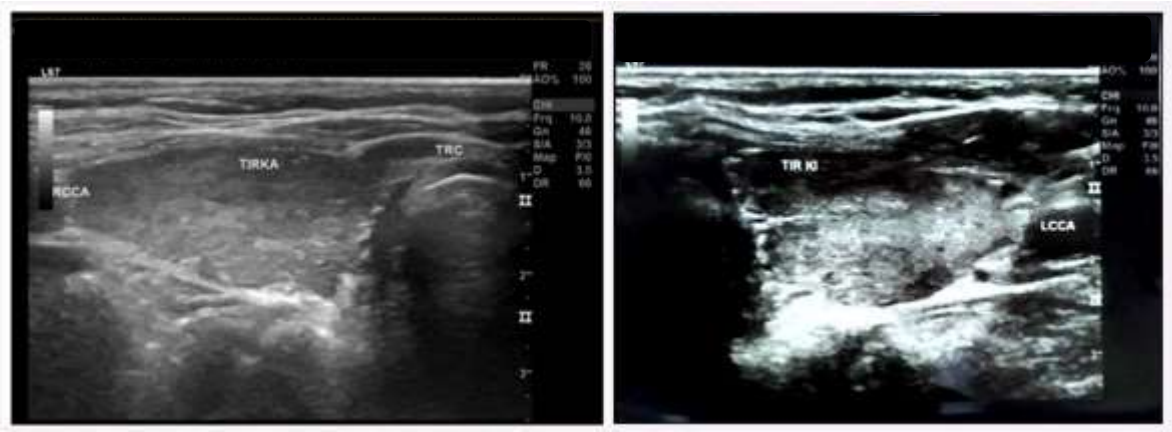

Figure 2. Ultrasound of the thyroid gland.

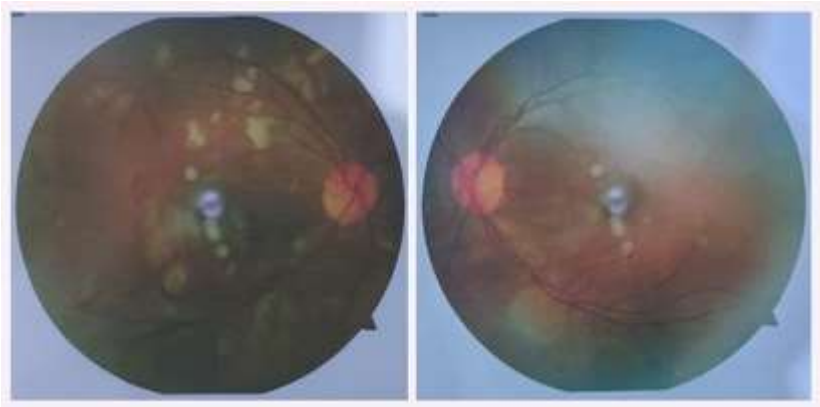

Figure 3. Eye funduscopy.

3. Discussion

Drug-induced lupus erythematosus (DILE) is a unique and often challenging medical condition that presents a clinical picture similar to systemic lupus erythematosus (SLE), but with a crucial distinction, its onset is directly linked to exposure to certain medications. This intricate condition, arising from the complex interplay between genetics, immunity, and pharmacology, underscores the profound impact of drugs on the human body and its delicate immune balance. DILE is characterized by a constellation of symptoms that often mirror those seen in SLE, including fatigue, joint pain, skin rashes, and fever. However, unlike SLE, which is a chronic autoimmune disease, DILE typically resolves upon discontinuation of the offending medication. This reversibility highlights the causative role of the drug in triggering the immune dysregulation that underlies the condition. The prevalence of DILE remains uncertain, with estimates suggesting that it accounts for approximately 10-15% of all lupus cases. However, the true incidence may be higher, as many cases may go unrecognized or be misdiagnosed as idiopathic SLE. The clinical spectrum of DILE is broad, ranging from mild, self-limiting symptoms to severe, life-threatening complications. The most commonly reported manifestations include arthralgia, myalgia, fever, and serositis. Renal and neurological involvement are less frequent but can occur in some cases. The exact mechanisms underlying the development of DILE remain an area of active research and scientific inquiry, and significant progress has been made in understanding the key players and pathways involved in this intriguing disorder. The genetic component of DILE susceptibility is evident from the observation that certain genetic polymorphisms are associated

with an increased risk of developing the condition. These genetic variations may influence various aspects of drug metabolism, immune regulation, and inflammatory responses, making individuals more prone to developing DILE upon exposure to certain medications. One of the most well-studied genetic associations with DILE is the HLA (human leukocyte antigen) system. HLA genes encode proteins that play a crucial role in immune recognition and self-tolerance. Specific HLA alleles, such as HLA-DR2 and HLA-DR3, have been linked to an increased risk of DILE, particularly in individuals exposed to drugs such as hydralazine and procainamide. These HLA alleles may influence the presentation of drug-modified antigens to T cells, triggering an autoimmune response. Other genetic variations outside the HLA system have also been implicated in DILE susceptibility. Polymorphisms in genes involved in drug metabolism, such as CYP2D6 and NAT2, may affect the way drugs are processed and cleared from the body, potentially leading to the accumulation of reactive metabolites that can trigger immune dysregulation. Additionally, variations in genes involved in immune regulation, such as TNF-alpha and IL-6, may contribute to the inflammatory response seen in DILE. Some drugs can directly stimulate immune cells, leading to the production of autoantibodies and inflammation. For example, hydralazine, a vasodilator used to treat hypertension, can directly activate B cells, promoting the production of anti-histone antibodies. Certain drugs can modify self-antigens, making them appear foreign to the immune system and triggering an autoimmune response. Procainamide, an antiarrhythmic drug, can acetylate histones, altering their structure and making them immunogenic. Some drugs can interfere with the mechanisms that maintain immune tolerance, leading to the recognition and attack of self-tissues. For instance, minocycline, an antibiotic, can inhibit T regulatory cells, which play a crucial role in suppressing autoimmune responses. Environmental triggers, such as ultraviolet radiation and infections, may also play a role in the development of DILE. These triggers can exacerbate immune dysregulation and contribute to the onset of symptoms. Ultraviolet radiation can induce DNA damage and apoptosis, leading to the release of self-antigens that can trigger autoimmune responses. Infections can activate the immune system and promote inflammation, potentially contributing to the development of DILE in susceptible individuals. In the presented case, the patient's history of methimazole use, along with the development of lupus-like symptoms such as fever, joint pain, and skin rash, strongly suggested DILE. The temporal relationship between the initiation of methimazole and the onset of symptoms, along with the absence of lupus-related manifestations prior to drug exposure, further supported the diagnosis. Methimazole, a commonly used antithyroid drug, is a rare but recognized cause of DILE. The incidence of methimazole-induced DILE is estimated to be around 0.1-0.2%. The clinical presentation is typically similar to that of DILE induced by other drugs, with musculoskeletal symptoms, skin rashes, and serositis being the most common manifestations. The exact mechanism by which methimazole induces DILE is not fully understood. However, it is postulated that drug-mediated changes in the structure of the DNA-histone complex may play a role. These changes can render histones less hydrolysable, increasing their immunogenicity and potentially exposing new epitopes. DILE typically presents with a constellation of symptoms that mimic those of SLE, making the diagnostic process challenging. The diagnosis of DILE relies on a combination of clinical findings, laboratory investigations, and a thorough medication history. The cornerstone of DILE management is the prompt identification and withdrawal of the causative medication. In most cases, this leads to a significant improvement in symptoms and laboratory abnormalities. However, some patients may require additional treatment with corticosteroids or immunosuppressive agents to control disease activity. The prognosis for DILE is generally favorable, with most patients experiencing resolution of symptoms upon discontinuation of the offending drug. However,

some patients may develop chronic lupus-like symptoms or complications. Regular monitoring and follow-up are essential to ensure early detection and management of any long-term effects. The most crucial step in managing DILE is to immediately stop the medication that triggered the condition. This often leads to a gradual resolution of symptoms and laboratory abnormalities over several weeks to months. In some cases, symptoms may improve rapidly within days of stopping the drug. For patients with mild symptoms such as arthralgia or myalgia, NSAIDs can provide relief from pain and inflammation. In cases of moderate to severe DILE, with significant systemic involvement or organ damage, corticosteroids are often necessary to suppress the immune response and control inflammation. The dosage and duration of corticosteroid therapy are individualized based on the severity of the disease and the patient's response to treatment. In patients with severe or refractory DILE, immunosuppressive agents such as azathioprine or mycophenolate mofetil may be considered. These medications help to further suppress the immune system and prevent long-term complications. Hydroxychloroquine, an antimalarial drug, is often used in the management of DILE, particularly for skin and joint manifestations. It has also been shown to reduce the risk of flares and improve long-term outcomes. Regular monitoring is essential to assess the response to treatment and detect any potential complications. This may include periodic blood tests, urine tests, and imaging studies. Patients should be educated about the potential long-term effects of DILE and the importance of follow-up care. The prognosis for DILE is generally favorable, with most patients experiencing complete resolution of symptoms upon discontinuation of the offending drug. Patients with more severe manifestations or organ involvement may have a longer recovery time and a higher risk of complications. Early diagnosis and prompt discontinuation of the offending drug are associated with a better prognosis. Patients with a pre-existing autoimmune condition may be more prone to developing chronic lupus-like symptoms or complications. The type of drug and duration of exposure can influence the severity and course of DILE. In the presented case, the patient's history of methimazole use, along with the development of lupus-like symptoms such as fever, joint pain, and skin rash, strongly suggested DILE. The temporal relationship between the initiation of methimazole and the onset of symptoms, along with the absence of lupus-related manifestations prior to drug exposure, further supported the diagnosis. Methimazole, a commonly used antithyroid drug, is a rare but recognized cause of DILE. The incidence of methimazole-induced DILE is estimated to be around 0.1-0.2%. The clinical presentation is typically similar to that of DILE induced by other drugs, with musculoskeletal symptoms, skin rashes, and serositis being the most common manifestations. The exact mechanism by which methimazole induces DILE is not fully understood. However, it is postulated that drug-mediated changes in the structure of the DNA-histone complex may play a role. These changes can render histones less hydrolysable, increasing their immunogenicity and potentially exposing new epitopes.[11,12]

Graves' disease, a prevalent autoimmune disorder, arises from a complex interplay of genetic and environmental factors, leading to the overproduction of thyroid hormones (hyperthyroidism). This intricate condition, named after the Irish physician Robert Graves who first described it in the 19th century, is characterized by a spectrum of clinical manifestations, including palpitations, heat intolerance, weight loss, anxiety, and in some cases, ophthalmopathy (eye disease) and dermopathy (skin disease). At its core, Graves' disease is driven by the aberrant production of autoantibodies, specifically thyroid-stimulating immunoglobulins (TSIs), that mimic the action of thyroid-stimulating hormone (TSH). These autoantibodies bind to and activate the TSH receptor on thyroid follicular cells, leading to uncontrolled synthesis and release of thyroid hormones, primarily thyroxine (T4) and triiodothyronine (T3). The prevalence of Graves' disease varies across

populations, with an estimated prevalence of 0.5% to 2.0% in women and a female-to-male ratio of approximately 10:1. The peak incidence occurs between the ages of 30 and 50, although it can affect individuals of all ages. The pathogenesis of Graves' disease involves a complex interplay of genetic susceptibility, environmental triggers, and immune dysregulation. A family history of Graves' disease or other autoimmune disorders increases the risk of developing the condition. Specific genes within the HLA (human leukocyte antigen) system, such as HLA-DR3, have been strongly associated with Graves' disease susceptibility. Viral or bacterial infections may trigger or exacerbate autoimmune responses in genetically predisposed individuals. Psychological or physical stress can disrupt immune homeostasis and contribute to the development of autoimmune diseases. Cigarette smoking has been shown to increase the risk of Graves' disease and Graves' ophthalmopathy. Excessive iodine intake can trigger or worsen hyperthyroidism in susceptible individuals. The hallmark of Graves' disease is the loss of immune tolerance to thyroid antigens, leading to the production of TSIs. These autoantibodies bind to and activate the TSH receptor on thyroid follicular cells, leading to uncontrolled synthesis and release of thyroid hormones. The clinical presentation of Graves' disease is diverse, ranging from subtle symptoms to life-threatening complications. The excessive production of thyroid hormones leads to a hypermetabolic state, characterized by palpitations, heat intolerance, weight loss, tremors, anxiety, insomnia, increased appetite, and frequent bowel movements. An inflammatory condition affecting the tissues surrounding the eyes, causing proptosis (bulging eyes), diplopia (double vision), eye irritation, photophobia (sensitivity to light), and periorbital edema (swelling around the eyes) The diagnosis of Graves' disease is based on a combination of clinical findings, laboratory investigations, and imaging studies. A thorough medical history and physical examination are essential to assess for symptoms and signs of hyperthyroidism and Graves' ophthalmopathy. Elevated free T4 and suppressed TSH levels are characteristic of hyperthyroidism. The presence of TSIs confirms the diagnosis of Graves' disease. A RAIU scan can help differentiate Graves' disease from other causes of hyperthyroidism. An ultrasound of the thyroid gland can assess its size, shape, and blood flow. The treatment of Graves' disease aims to control hyperthyroidism and alleviate symptoms. Antithyroid drugs, such as methimazole and propylthiouracil (PTU), inhibit the synthesis of thyroid hormones. Radioactive iodine therapy destroys thyroid tissue, leading to a reduction in thyroid hormone production. Surgical removal of the thyroid gland (thyroidectomy) is an option for patients who do not respond to or are not candidates for other treatments. The prognosis for Graves' disease is generally good, with most patients achieving remission with appropriate treatment. However, some patients may experience recurrent hyperthyroidism or develop complications such as thyroid storm or ophthalmopathy. Regular monitoring and follow-up are essential to ensure early detection and management of any long-term effects. In the presented case, the patient's history of palpitations, heat intolerance, and other hyperthyroid symptoms, along with the presence of elevated free T4 and suppressed TSH levels, confirmed the diagnosis of Graves' disease. The patient was initially treated with methimazole, but due to the development of DILE, she was switched to PTU. The coexistence of Graves' disease and DILE in this patient highlights the complex interplay between autoimmune diseases and drug-induced complications. Further research is needed to better understand the mechanisms underlying these conditions and develop more effective treatment strategies.[13,14]

Primary infertility, defined as the inability to conceive after one year of unprotected intercourse without any prior pregnancies, is a complex and often emotionally challenging condition that affects millions of couples worldwide. It represents a significant public health concern, with an estimated prevalence of 2% to 5% among reproductive-aged couples. The causes of

primary infertility are multifaceted, stemming from a complex interplay of female factors, male factors, and unexplained factors. In many cases, infertility is attributed to a combination of factors, requiring a comprehensive evaluation to identify the underlying cause and guide appropriate treatment. Problems with ovulation, the release of an egg from the ovary, account for a significant proportion of female infertility cases. These disorders can range from infrequent ovulation (oligoovulation) to complete absence of ovulation (anovulation). Common causes of ovulatory disorders include polycystic ovary syndrome (PCOS), hypothalamic dysfunction, hyperprolactinemia, and premature ovarian insufficiency. Damage or blockage of the fallopian tubes, which transport the egg from the ovary to the uterus, can impede the meeting of sperm and egg, preventing fertilization. Common causes of tubal factor infertility include pelvic inflammatory disease (PID), endometriosis, and previous ectopic pregnancy. Abnormalities in the structure or lining of the uterus can hinder the implantation of the fertilized egg or increase the risk of miscarriage. Common uterine factors include fibroids, polyps, adenomyosis, and uterine anomalies. The cervix, the lower part of the uterus, produces mucus that helps sperm travel to the egg. Abnormalities in cervical mucus or the presence of cervical stenosis (narrowing of the cervical canal) can impede sperm transport and reduce fertility. Female fertility naturally declines with age, particularly after the age of 35. This decline is attributed to a decrease in the number and quality of eggs, as well as an increased risk of age-related complications such as miscarriage and chromosomal abnormalities. Abnormalities in sperm production, function, or delivery can significantly impair fertility. Common sperm disorders include low sperm count (oligospermia), poor sperm motility (asthenospermia), abnormal sperm morphology (teratospermia), and azoospermia (absence of sperm). A varicocele is an enlargement of the veins within the scrotum, which can impair sperm production and function due to increased testicular temperature. Problems with ejaculation, such as retrograde ejaculation (ejaculate entering the bladder instead of exiting the penis) or premature ejaculation, can hinder sperm delivery to the female reproductive tract. Blockage of the reproductive ducts can prevent sperm from being released during ejaculation. Common causes of obstructive azoospermia include infections, congenital abnormalities, and vasectomy. Genetic abnormalities, such as Klinefelter syndrome or Y chromosome microdeletions, can impair sperm production and lead to infertility. In some cases, despite a comprehensive evaluation, no specific cause for infertility can be identified. This is referred to as unexplained infertility and accounts for a significant proportion of infertility cases. The evaluation of primary infertility typically involves a combination of medical history, physical examination, and specialized tests. A detailed medical history, including menstrual history, sexual history, and previous pregnancies, is essential to identify potential risk factors and guide further evaluation. A physical examination, including a pelvic exam for women and a testicular exam for men, can help identify any anatomical abnormalities or signs of underlying medical conditions. Ovulation testing, including basal body temperature charting, ovulation predictor kits, and blood tests, can assess whether ovulation is occurring regularly. An HSG is an X-ray procedure that evaluates the fallopian tubes for blockage or abnormalities. Laparoscopy is a minimally invasive surgical procedure that allows visualization of the pelvic organs and can identify conditions such as endometriosis or pelvic adhesions. Semen analysis evaluates the quantity, quality, and motility of sperm. Hormone testing, including thyroid function tests, prolactin levels, and testosterone levels, can assess for hormonal imbalances that may contribute to infertility. The treatment of primary infertility depends on the underlying cause and may involve a combination of lifestyle modifications, medications, surgery, and assisted reproductive technologies (ART). Lifestyle modifications, such as weight loss, smoking cessation, and stress management, can improve fertility in some cases. Medications, such as ovulation

induction agents and hormone therapies, can help regulate ovulation and improve sperm production. Surgical procedures, such as laparoscopic removal of endometriosis or repair of tubal blockage, can address anatomical abnormalities that contribute to infertility. ART procedures, such as in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI), involve manipulating eggs and sperm in a laboratory setting to achieve fertilization and embryo transfer. The prognosis for primary infertility varies depending on the underlying cause, the age of the couple, and the chosen treatment approach. With advances in reproductive medicine, many couples with primary infertility are able to achieve successful pregnancies. However, infertility can be a challenging and emotionally taxing journey, requiring patience, perseverance, and emotional support. In the presented case, the patient's history of primary infertility, despite being married for 16 years and actively attempting to become pregnant, suggests a possible underlying reproductive disorder. The coexistence of primary infertility and DILE raises the question of a possible link between these conditions. While there is no definitive evidence linking DILE to primary infertility, some studies have suggested a possible association between autoimmune diseases and reproductive difficulties. It is conceivable that the underlying autoimmune dysregulation contributing to DILE could also affect reproductive function. However, further research is needed to elucidate the complex interplay between these conditions.[15,16]

The coexistence of DILE, Graves' disease, and primary infertility in the presented case raises intriguing questions about the intricate interplay between these conditions. While no definitive evidence directly links DILE or Graves' disease to primary infertility, emerging research suggests a possible association between autoimmune diseases and reproductive difficulties. Autoimmune diseases, characterized by the immune system mistakenly attacking the body's tissues, have been linked to various reproductive health issues, including infertility, miscarriage, and preterm birth. The underlying mechanisms connecting these conditions are complex and multifaceted, involving hormonal imbalances, inflammation, and direct effects on reproductive organs. Autoimmune diseases affect millions of people worldwide, with women disproportionately affected. These conditions can have a profound impact on reproductive health, affecting fertility, pregnancy outcomes, and overall well-being. Studies have shown that women with autoimmune diseases have a higher risk of infertility compared to the general population. The prevalence of infertility among women with autoimmune diseases varies depending on the specific condition, but it is estimated to be between 10% and 30%. Moreover, autoimmune diseases can increase the risk of miscarriage, preterm birth, and other pregnancy complications. Women with autoimmune diseases are also more likely to experience difficulties with breastfeeding and postpartum depression. The mechanisms underlying the association between autoimmune diseases and reproductive health issues are complex and not fully understood. Autoimmune diseases can disrupt the delicate hormonal balance necessary for reproduction. For example, in Graves' disease, the overproduction of thyroid hormones can interfere with ovulation and menstrual cycles. In Hashimoto's thyroiditis, an autoimmune condition characterized by hypothyroidism, the underproduction of thyroid hormones can also disrupt reproductive function. Chronic inflammation, a hallmark of autoimmune diseases, can create a hostile environment for conception and implantation. Inflammation can affect the quality of eggs and sperm, impair tubal function, and disrupt endometrial receptivity. Autoimmune diseases can directly target reproductive organs, leading to structural damage or functional impairment. For example, autoimmune oophoritis (inflammation of the ovaries) can lead to premature ovarian insufficiency and infertility. Autoimmune orchitis (inflammation of the testes) can impair sperm production and lead to male infertility. Antiphospholipid antibodies, commonly found in autoimmune diseases like lupus, can increase the risk

of blood clots, which can impair placental function and lead to miscarriage or pregnancy complications. Both DILE and Graves' disease are autoimmune disorders, suggesting a shared predisposition to immune dysregulation. It is conceivable that the same genetic and environmental factors contributing to the development of these conditions could also affect reproductive function. Autoimmune diseases can disrupt the delicate hormonal balance necessary for reproduction. For example, in Graves' disease, the overproduction of thyroid hormones can interfere with ovulation and menstrual cycles. Chronic inflammation, a hallmark of autoimmune diseases, can create a hostile environment for conception and implantation. Inflammation can affect the quality of eggs and sperm, impair tubal function, and disrupt endometrial receptivity. Autoimmune diseases can directly target reproductive organs, leading to structural damage or functional impairment. For example, autoimmune oophoritis (inflammation of the ovaries) can lead to premature ovarian insufficiency and infertility. Antiphospholipid antibodies, commonly found in autoimmune diseases like lupus, can increase the risk of blood clots, which can impair placental function and lead to miscarriage or pregnancy complications. In the presented case, the patient's history of primary infertility, despite being married for 16 years and actively attempting to become pregnant, suggests a possible underlying reproductive disorder. The coexistence of primary infertility with both DILE and Graves' disease raises the possibility that autoimmune dysregulation may be contributing to her reproductive difficulties. It is conceivable that the same immune system abnormalities responsible for her DILE and Graves' disease could also be affecting her fertility. For example, inflammation associated with these conditions could be impairing her ovarian function or creating a hostile environment for implantation.[17,18]

The management of a patient with the trifecta of DILE, Graves' disease, and primary infertility necessitates a multifaceted approach that addresses each condition individually while acknowledging their potential interplay and impact on overall health. This intricate scenario demands a coordinated effort between specialists, including endocrinologists, rheumatologists, immunologists, and fertility specialists, to optimize treatment outcomes and minimize potential complications. The cornerstone of DILE management is the prompt identification and withdrawal of the offending medication. In this case, methimazole, commonly used to treat Graves' disease, was identified as the trigger for DILE and was immediately discontinued. This step is crucial in halting the progression of DILE and facilitating the resolution of symptoms. Following the withdrawal of methimazole, alternative antithyroid medications, such as propylthiouracil (PTU), may be considered to manage Graves' disease. However, careful monitoring is essential as PTU carries a small risk of inducing DILE as well. Non-steroidal anti-inflammatory drugs (NSAIDs) to alleviate joint pain and inflammation. Corticosteroids to suppress the immune response and control systemic inflammation in moderate to severe cases. Immunosuppressive agents such as azathioprine or mycophenolate mofetil may be necessary in severe or refractory cases. Hydroxychloroquine, an antimalarial drug, is often employed for its immunomodulatory effects, particularly for skin and joint manifestations. Antithyroid medications like methimazole or PTU to inhibit thyroid hormone synthesis. However, in this case, methimazole was discontinued due to DILE, and PTU requires careful monitoring. Radioactive iodine therapy to ablate overactive thyroid tissue, leading to a reduction in thyroid hormone production. This option may be considered if antithyroid medications are not tolerated or effective. Surgery (thyroidectomy) for patients who do not respond to or are not candidates for other treatments. Addressing primary infertility requires a comprehensive evaluation to identify the underlying cause, which may be multifactorial. In this case, further investigations are needed to assess ovarian function, tubal patency, and other potential contributing factors. Lifestyle modifications such as weight loss, stress

management, and smoking cessation. Ovulation induction agents to stimulate ovulation in cases of ovulatory disorders. Hormone therapies to correct hormonal imbalances. Surgical interventions to address anatomical abnormalities, such as endometriosis or tubal blockage. Assisted reproductive technologies (ART) such as in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) may be considered if other treatments are unsuccessful. The coexistence of DILE, Graves' disease, and primary infertility requires careful consideration of the interplay between these conditions. The presence of multiple autoimmune diseases suggests a heightened state of immune dysregulation, which may necessitate more aggressive immunosuppressive therapy. The potential for drug interactions between medications used to treat each condition must be carefully evaluated. The effects of DILE and Graves' disease on fertility should be considered when planning infertility treatment. Regular monitoring and follow-up are crucial to assess treatment response, manage potential complications, and optimize long-term outcomes. Periodic blood tests to monitor thyroid function, autoimmune markers, and potential drug-related side effects. Urine tests to assess for renal involvement in DILE. Imaging studies such as ultrasound or echocardiography to evaluate organ function. Fertility assessments to monitor ovarian function and guide infertility treatment. The prognosis for patients with coexisting DILE, Graves' disease, and primary infertility is multifaceted and depends on various factors, including the severity of each condition, individual response to treatment, and potential interactions between the conditions. Generally, the prognosis for DILE is favorable. Most patients experience complete resolution of symptoms upon discontinuation of the offending drug. Even after discontinuing the causative medication, some patients may experience lingering fatigue and joint pain, which can impact their quality of life. In rare cases, DILE can lead to organ damage, such as kidney or heart involvement, which can have long-term health consequences. Patients with DILE may have an increased risk of developing other autoimmune diseases, such as lupus or rheumatoid arthritis. The prognosis for Graves' disease is also generally good, with most patients achieving remission with appropriate treatment. Even after successful treatment, some patients may experience recurrent episodes of hyperthyroidism, requiring ongoing management. This eye condition, characterized by bulging eyes, double vision, and other eye-related symptoms, can persist even after hyperthyroidism is controlled. A rare but life-threatening complication of Graves' disease, characterized by a sudden and severe worsening of hyperthyroid symptoms. The prognosis for primary infertility varies depending on the underlying cause. Female fertility declines with age, particularly after 35, making it more challenging to conceive. The specific cause of infertility can significantly impact the chances of successful conception. The chosen treatment approach, such as lifestyle modifications, medications, surgery, or assisted reproductive technologies, can influence the likelihood of pregnancy. The coexistence of DILE, Graves' disease, and primary infertility adds another layer of complexity to the prognosis. The interplay between these conditions can influence treatment decisions and outcomes. The presence of multiple autoimmune diseases may necessitate more aggressive immunosuppressive therapy, which can have potential side effects and impact overall health. The potential for drug interactions between medications used to treat each condition must be carefully considered. DILE and Graves' disease can both affect fertility, making it essential to address these conditions effectively to optimize the chances of conception.[19,20]

4. Conclusion

This case underscores the importance of recognizing and managing DILE in patients receiving antithyroid medications, particularly methimazole. The complex interplay between DILE, Graves' disease, and primary infertility necessitates a multifaceted treatment approach and ongoing monitoring.

5. References

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