Antithyroid Drug-Induced Lupus Erythematosus and Immunoglobulin A Deficiency

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Conflict of interest: None declared

Patient: Male, 32-year-old
Final Diagnosis: Drug induced lupus erythematosus
Symptoms: Lymphadenopathy • proteinuria • rash
Medication: —
Clinical Procedure: Renal biopsy
Specialty: Endocrinology and Metabolic • Immunology • General and Internal Medicine

Objective: Rare co-existence of disease or pathology
Background: Antithyroid drugs, namely methimazole, are well-known causes of drug-induced lupus erythematosus. This is, however, an infrequent adverse effect. Selective Immunoglobulin A (IgA) deficiency, in contrast, is the most common primary immunodeficiency. Patients with IgA deficiency are at risk of developing infectious diseases, but also autoimmune diseases such as Grave's disease or systemic lupus erythematosus.

Case Report: We report a case of methimazole-induced lupus erythematosus in a 32-year-old man with renal involvement and concomitant selective IgA deficiency. Symptoms promptly resolved after treatment with hydroxychloroquine and corticosteroids after discontinuation of methimazole. Lupus nephritis required treatment with cyclophosphamide followed by maintenance therapy with mycophenolate mofetil.

Conclusions: Drug-induced lupus erythematosus usually develops after a few months or years of exposure to the causative agent. No specific symptoms exist. The diagnosis is not based on particular specific tests, but relies on a set of arguments evoking the role of the medication inducing the condition. The first step in treatment is to stop the causative drug. The therapeutic management of the various manifestations does not differ from that of idiopathic systemic lupus erythematosus. We briefly discuss the relationship between drug-induced lupus erythematosus, Grave's disease, and IgA deficiency, and suggest that IgA deficiency may act as a potential risk factor. Testing for IgA deficiency could be helpful in patients being treated with drugs known to be associated with drug-induced lupus erythematosus.

MeSH Keywords: IgA Deficiency • Lupus Erythematosus, Systemic • Methimazole

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**Background**

Methimazole is often used as a first-line treatment for hyperthyroidism. Drug-induced lupus erythematosus (DILE) is an infrequent adverse effect [1]. The criteria used for the diagnosis of DILE are: (1) exposure to a medication known to be associated with DILE; (2) absence of a clinical history of systemic lupus erythematosus (SLE) before initiation of the medication; (3) presence of antinuclear antibodies (ANA) and clinical symptoms compatible with SLE; (4) clinical improvement and progressive lowering of ANA titers after discontinuation of the causative drug [2–4]. The first step in the management of DILE is to stop the causative drug. The treatment of specific manifestations does not differ from idiopathic SLE [2,3].

**Case Report**

A 32-year-old man presented with a 2-week duration persistent fever associated with night sweats. Ten days before, a blood test had shown leucopenia and hypoalbuminemia. Urinary analysis showed proteinuria and active sediment. During childhood, the patient had experienced recurrent tonsillitis. His past history was notable for Graves' hyperthyroidism. For which treatment with methimazole had been initiated 5 months prior to his initial visit at our hospital. The diagnosis had been confirmed by a positive test for thyrotropin-receptor autoantibodies (TRAbs). A urine dipstick at that time showed no proteinuria. Physical examination revealed a temperature of 39.6°C. A malar rash was present. Lymphadenopathy was noted in the cervical, supraclavicular, axillary, and inguinal areas, along with splenomegaly. In addition to fever and night sweats, the patient reported weight loss of 7 kg, diffuse arthralgia, and Raynaud’s phenomenon.

Laboratory investigations were performed. Serologies were negative for *Brucella*, *Treponema*, *Bartonella*, HIV, HBV, HCV, EBV, Parvovirus, CMV, and HSV. Immunophenotyping of peripheral blood lymphocytes was unremarkable. Other laboratory tests showed recent onset of lymphopenia (absolute count 1070 per cubic millimeter), mild anemia (12 g per deciliter), and elevated erythrocyte sedimentation rate with only mild elevation of C-reactive protein, hypoalbuminemia, and hyperthyroidism. Testing for ANA was positive at 1: 1280, with a homogenous pattern. Further identification showed positive anti-dsDNA (1123 U/mL), anti-nucleosome, and anti-histone antibodies, as well as anti-cardiolipin antibodies. Serum protein electrophoresis showed polyclonal hypergammaglobulinemia with an elevated IgG level (19.99 g per deciliter; reference range 7 to 16) and IgA deficiency (IgAD) (less than 0.20 g per deciliter; reference range 0.7 to 4). A Coombs test (direct antiglobulin test) was positive, without evidence of hemolysis. Complement levels (C3 and C4) were low. Circulating immune complexes and low levels of cryoglobulins were detected. Glomerular filtration rate was normal but urinalysis showed proteinuria (2.5 g/day) with predominant albuminuria. No infectious disease was detected. A diagnosis of systemic lupus erythematosus was made on the basis of the 2019 European League Against Rheumatism/American College of Rheumatology criteria [5].

Methimazole is known as a potential causative drug of DILE and was stopped. Treatment with hydroxychloroquine and angiotensin-converting enzyme inhibitor was initiated, while waiting for the results of renal and lymph node biopsies. Proteinuria worsened (7 g/day) and the patient developed leg edema. The renal biopsy specimen was consistent with class IV lupus nephritis. Treatment with glucocorticoids and intravenous cyclophosphamide was begun, leading to complete resolution of lymphadenopathy and cutaneous manifestations. Repeated laboratory evaluation showed progressive improvement of anemia and disappearance of leucopenia, hypergammaglobulinemia, and cryoglobulins.

After 6 months, maintenance therapy with mycophenolate mofetil was begun and therapy with glucocorticoids was slowly tapered. Proteinuria improved out of the nephrotic range, and complement and ANA levels normalized. Anti-histone antibodies were no longer detected and laboratory tests for them were repeatedly negative thereafter.

**Discussion**

Methimazole is often used as a first-line treatment for hyperthyroidism. DILE is an infrequent adverse effect [1], and accounts for 5% to 10% of SLE cases. DILE usually develops after a few months or years of exposure to the causative agent. No symptoms are pathognomonic; the most frequent are myalgia, arthralgia, arthritis, and constitutional symptoms such as fever, anorexia, and weight loss [2]. Renal and neurological involvement is uncommon [2,3].

Immunologic characteristics include positive ANA in 90% of cases [3], most often with a homogeneous nuclear staining pattern on fluorescence. Anti-histone antibodies are found in more than 75% of patients with DILE and in only 20% of classical cases of SLE [4]. The presence of anti-histone antibodies should be taken into consideration for DILE in a patient with features suggestive of SLE, although anti-dsDNA antibodies are most often absent.

When renal involvement is present, renal biopsy should be performed. Histological and immunofluorescence features do not differ from those observed in classical SLE.
The management of DILE is to stop the causative drug. The treatment of specific manifestations does not differ from that of idiopathic SLE [2,3].

Dysgammaglobulinemia is a frequent feature in patients with SLE. Polyclonal hypergammaglobulinemia is common, and is related to the inflammatory activity of the disease. On the other hand, some patients may exhibit hypogammaglobulinemia. In this case, the etiology is most often iatrogenic (corticosteroids, immunosuppressive drugs, B-cell targeting therapies) or related to renal disease in patients with nephrotic-range proteinuria, but primary immunoglobulin deficiency is also possible [6].

Selective IgAD is frequent in the general population, and may indeed co-exist in some patients with SLE. The clinical presentation does not seem to differ between SLE patients with concomitant IgAD and those without concomitant IgAD [7]. While most patients with IgAD remain asymptomatic, some develop infectious or autoimmune manifestations such as autoimmune thyroid disorders.

Graves’ disease is characterized by the presence of TRAbs. Studies have shown a significant association between positivity for TRAbs and IgAD [8]. To our knowledge, no association has been described between IgAD and DILE, although some studies report an association between IgAD and SLE. This association could reflect a common underlying genetic background rather than a causal relationship. Major histocompatibility haplotypes HLA-B8, DR3, and DQ2 are indeed strongly associated with both IgAD, Graves’ disease, and SLE [8].

Our patient was known to have IgAD, which might have put him at risk for developing both Graves’ disease and DILE after exposure to methimazole.

Conclusions

We here present a patient with concomitant IgAD and Graves’ disease who further developed DILE when exposed to methimazole. Further studies are needed to confirm that IgAD might be considered as a risk factor for both DILE and Graves’ disease. If confirmed, screening patients for immunoglobulin deficiency might be a simple way for physicians to prevent these types of potential adverse effects from lupus-inducing drugs.

Department and Institution where work was done

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