

Methimazole-induced lupus erythematosus: a case report

Li-Chieh Wang, Wen-Yu Tsai, Yao-Hsu Yang, Bor-Luen Chiang

Department of Pediatrics, National Taiwan University Hospital, Taipei, Taiwan, ROC

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A 15-year-old girl had a history of diffuse goiter and received methimazole treatment 2 months before admission to the hospital. She developed bilateral lower leg edema 5 days before admission and the laboratory examinations revealed leukopenia, anemia, proteinuria, and granular cast. Positive antinuclear antibodies and anti-double strand (anti-ds) DNA antibodies were noted, although complement levels were not reduced. Myeloperoxidase antineutrophil cytoplasmic antibody was positive. A renal biopsy disclosed that there was focal segmental glomerulosclerosis. Methimazole was discontinued, and she was treated with prednisolone and Plaquenil, after which the symptoms and laboratory tests became normal within 40 days. The prednisolone was discontinued after treatment for seven months. Currently, the anti-dsDNA, C3, C4, CBC, urinalysis, and thyroid function tests are within normal limits. With hydroxychloroquine and levothyroxine, she was free of symptoms after discontinuation of methimazole until now (about 21 months).

Key words: Autoimmune thyroiditis, drug-induced lupus erythematosus, methimazole

Methimazole is one of the thioureylene types of antithyroid drugs, an inhibitor of the iodide "organification" process. The well-known complications of these compounds include agranulocytosis [1], skin rash [2] and teratogenicity [3], thrombocytopenia, acute hepatic necrosis, cholestatic hepatitis, arthralgia, abnormalities of taste and smell, and drug-induced lupus erythematosus (DILE) [4]. Among them, the drug most commonly reported to cause DILE is propylthiouracil [5]. We report a rare case of a patient who had involvement in methimazole-induced lupus erythematosus. The few cases of methimazole-induced lupus-like syndrome that have been recorded in the literature are also reviewed.

Case Report

A 15-year-old girl was reported to have a diffuse goiter since she was 5 years old. Her thyroid function and aspiration cytology were within normal limits at that time. Grade I thyroid enlargement was detected when she was 8 years old, and laboratory tests showed T3 157 ng/dL, T4 9.8 µg/dL, TSH 0.9 µIU/mL, anti-microsomal antibodies (AMA) 1:40 (–), anti-thyroglobulin antibodies (ATA) 1:40 (–), and thyroid-binding inhibiting immunoglobulin (TBII) negative. Because of this, simple goiter was then impressed. The

AMA 1:320 (+) was detected when she was 9 years old. By the time she was 11 years old, her local hospital suspected hyperthyroidism in spite of the fact that her thyroid function test was normal then. Propylthiouracil 300 mg/d was prescribed but she did not take the medication regularly and she did not return for a follow up appointment 3 months later. When she was 13 years old, grade III thyroid enlargement was detected and the laboratory tests showed T3 153 ng/dL, T4 9.8 µg/dL, TSH 1.9 µIU/mL, AMA 1:2560 (+), and ATA 1:40 (–). The thyroid echo disclosed a multinodular goiter with cystic change. The aspiration cytology revealed scanty follicular cells with colloid. Under the impression of autoimmune thyroiditis, levothyroxine 100 µg/day was given in the following 1.5 years. In addition, methimazole 20 mg/d was also given for 5 months by the local hospital during the same period of time. No side effects were noted then. The goiter later decreased to grade I when she was 14 years of age. When she was 15 years old, she visited the local hospital, when grade III thyroid enlargement was noted. Under the impression of hyperthyroidism, methimazole 10 mg/d and levothyroxine 100 µg/d were prescribed.

Two months later, she was admitted to our hospital. Unfortunately, 5 days before admission she was noted to have bilateral lower leg pitting edema and had suffered a weight loss of 3 to 4 kg/month. At admission, a physical examination showed that she had grade III diffuse goiter, with her spleen palpable at the tip, and bilateral lower leg pitting edema, but there was no evidence of hepatomegaly. Neither did she have a skin

Corresponding author: Dr. Bor-Luen Chiang, Department of Pediatrics, National Taiwan University Hospital, 7, Chung-Shan South Road, Taipei, Taiwan, 100, ROC. E-mail: gicmbor@ha.mc.ntu.edu.tw

rash nor oral ulcers. Also, she had no history of arthralgia. The laboratory examinations revealed the following data: white blood cell count (WBC) $1.4 \times 10^9/L$, hemoglobin 6.7 g/dL, platelet $237 \times 10^9/L$; urine protein 100 mg/dL (0.58 g/d), red blood cell count (RBC) 20 to 30/HPF, WBC 10-15/HPF, granular cast (+); albumin 3 mg/dL, globulin 5.8 mg/dL, blood urea nitrogen (BUN) 15.3 mg/dL, creatinine 0.7 mg/dL, triglyceride 134 mg/dL, cholesterol 101 mg/dL; clearance of creatinine 77.5 mL/min/1.73 m². The thyroid autoantibodies were AMA 1:160 (+), ATA 1:40 (-), TBII negative, and the thyroid function test showed T3 75.4 ng/dL, T4 <1 µg/dL, thyroid-stimulating hormone (TSH) 68.2 µIU/mL. The bone marrow aspiration revealed that she had only reactive bone marrow without malignant changes. The immunological study showed antinuclear antibodies (ANA) 1: 640 (+) speckle, C3 97 mg/dL, C4 14.7 mg/dL, erythrocyte sedimentation rate 1 h >130 mm and 2 h >160 mm, C-reactive protein 1.38 mg/dL, anti-double strand DNA (anti-dsDNA) 43.83 IU/mL, anti-RNP (-), anti-Sm (-), anti-SSA (-), anti-SSB (-), anti-SCL-70 (-), direct Coombs' test (++) , VDRL non-reactive, IgG 2810 mg/dL, IgM 331 mg/dL, anti-phospholipid antibody 4.798 IU/mL (normal <15 IU/mL), anti-cardiolipin antibody 31.376 IU/mL (normal <21 IU/mL), myeloperoxidase anti-neutrophil cytoplasmic antibody (ANCA) >100 U/mL (>15 U/mL positive), proteinase 3 ANCA 13.7 U/mL (7-15 U/mL borderline). The renal biopsy disclosed focal segmental glomerulosclerosis (Fig. 1). The microscopic examinations disclosed a mild focal

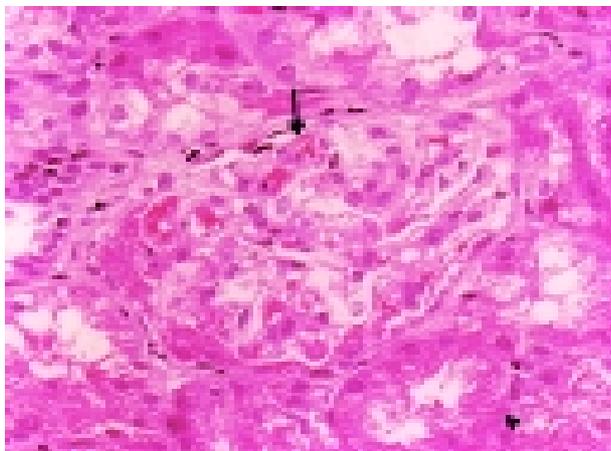


Fig. 1. Renal biopsy of focal segmental glomerulosclerosis. The microscopic examinations disclose mild focal increase in mesangial cellularity and matrix. Two glomeruli show segmental sclerosis and synechia (arrow). Focal tubular atrophy (arrow head) (5%) with mild interstitial fibrosis and focal chronic inflammatory cell infiltration are also noted. (hematoxylin & eosin stain; original magnification x200)

increase in mesangial cellularity and matrix. Two glomeruli showed segmental sclerosis and synechia. Focal tubular atrophy (5%) with mild interstitial fibrosis and focal chronic inflammatory cell infiltration were also noted. The periodic acid Schiff (PAS) and chromotrope silver methenamine (CSM) stains revealed no deposits. An immunofluorescent study demonstrated no deposition of IgA, IgG, IgM, C3, C1q, and properdin.

Under the impression of autoimmune thyroiditis and methimazole-induced LE, methimazole and levothyroxine were discontinued at admission. The thyroid function became normal 40 days later. Neutropenic fever was noted on the 4th day of admission and she received a 14-day course of antibiotic treatment. As she fulfilled the criteria of lupus erythematosus (positive ANA and anti-dsDNA, urinary casts, hemolytic anemia, and leukopenia), she received hydroxychloroquine 400 mg/d and prednisolone 60 mg/d since the 18th day of admission. Her urinalysis became normal at the 23rd day of admission and her CBC returned normal at the 40th day. The prednisolone was discontinued after treatment for 7 months. Currently, her anti-dsDNA, C3, C4, CBC, and urinalysis are within normal limits and her medication is changed to hydroxychloroquine 200 mg/d and levothyroxine 150 µg/d. The goiter decreases to grade II and the thyroid function test shows T3 106 ng/dL, T4 9.65 µg/dL, hsTSH <0.002 µIU/mL, free T4 1.73 µg/dL. She has been free of symptoms after discontinuation of methimazole until now (about 21 months).

Discussion

Lupus erythematosus is an autoimmune disorder and many drugs have been reported to cause a lupus-like syndrome called drug-induced lupus erythematosus (DILE) [5]. The diagnostic criteria for DILE include: (1) exposure to a drug suspected to induce DILE; (2) no history for systemic lupus erythematosus (SLE) prior to the use of the drug therapy; (3) detection of positive ANA with at least one clinical sign of SLE; (4) rapid improvement and gradual fall in the ANA and other serologic findings upon withdrawal of the drug [6]. The first case of DILE was reported in 1945 and was associated with sulfadiazine [7]. In the past, many drugs have been reported to be related to DILE. Among them, the drugs responsible for inducing DILE by well-controlled studies include hydralazine, procainamide, isoniazid, methyldopa, chlorpromazine, and quinidine [5]. Other drugs associated with DILE include sulfasalazine, anticonvulsants, antithyroid drugs, D-penicillamine, thiazide diuretics, and beta-blocking agents [5].

The characteristics of DILE do not vary according to gender [5]. Its clinical course is usually milder than idiopathic SLE and the involvement of the central nervous system (CNS) and kidneys has rarely been reported [8]. The most common symptoms are arthralgia (80%-90%) and myalgia (up to 50%) [5]. Skin manifestations appear in 25% to 53%, and these include erythema, erythema nodosum, papular skin lesions, and purpura [5]. Although CNS and renal involvements are rare, there were some drugs reported to be associated with renal involvement including D-penicillamine, hydralazine, propylthiouracil, procainamide, anticonvulsants, quinidine, and interferon gamma [9-11]. In immunological examinations, ANA are usually positive in DILE with autoantibodies against histones or single-stranded DNA [5]. Anti-ds DNA occur in less than 5% of patients with DILE [11]. Anti-Sm antibodies are absent in DILE [11]. Serum complements and immune complex levels are generally normal [9]. Our patient fulfilled the criteria of lupus erythematosus with

hemolytic anemia and leukopenia, mild proteinuria and urinary casts, positive ANA, negative anti-Sm, normal complement levels, but positive anti-dsDNA.

The pathogenesis of DILE includes (1) genetic factors; (2) drugs or compounds whose metabolites affect various components of the immune system; and (3) interactions of the implicated drugs or their metabolites, or both, with nuclear antigens [5]. Most symptoms of DILE are self-limiting once the offending drug has been discontinued, and conservative management such as nonsteroidal antiinflammatory drugs and a short course of low-dose prednisolone is recommended for resistant cases [10].

Among antithyroid agents, propylthiouracil is the first one known to induce DILE since 1952 and is most frequently reported to cause DILE [12]. This occurs by the propylthiouracil oxidizing to a reactive sulfonic acid metabolite. One of the intermediates is presumably a sulfenyl chloride, which is also chemically reactive and would react *in vivo* with protein sulfhydryl groups to

Table 1. Methimazole-induced lupus-like syndrome

Case no.	Age (yr)/sex	Drug/daily dose/duration	Clinical presentation	Laboratory finding	Outcome	Reference
1	17/F	MMI/30 mg/1 mo PTU/150 mg/1 wk	Fever, erythema and arthralgia; purplish-red erythema	Normal U/A, C3, C4, anti-ENA, LE latex (-), ANA 1:160 (+) speckle and homogeneous, anti-dsDNA (+), anti-ssDNA (+)	Resolved after DC MMI or PTU for days, recurred after re-challenge	[14]
2	15/F	MMI/60 mg/3 wk	Fever, arthritis, rash	LE preparation (+)	Resolved in 1 month while receiving PTU	[15]
3	14/F	PTU/200 mg/10 mo MMI/20 mg/18 d	Afebrile, rash, arthritis, persistent arthritis	ESR 44 mm, LE prep (-), ANA 1:160 (+), normal anti-DNA	Resolved in 72 h after DC MMI	[16]
4	13/F	PTU/200 mg/22 mo MMI/20 mg/3 wk	Afebrile, rash, arthritis; persistent polyarthritis	4 ESR 35 mm, LE prep (-), ANA 1:160 (+), normal anti-DNA	Resolved within 2 months after DC MMI	[16]
5	68/M	MMI/60-80 mg/ 1-2 wk	Diffuse rash and joint pains	No ANA data	Resolved after DC MMI	[17]
6	24/F	MMI/10 mg/4 yr	Fever, ulcer over legs	Leukocytopenia, ANA 1:2560 (+), anti-dsDNA (+), P-ANCA (+), ESR 82 mm, normal CH50, U/A and anti-Sm (-)	Resolved soon after DC MMI, normal lab data 2 months later	[18]
7	23/F	PTU/300 mg/11 d MMI/45 mg/2 wk	Fever, generalized rash; migrating polyarthritis, lymphadenopathy	WBC 3700, ANA 1:10 (+), anti-dsDNA 123U/mL, LE test (+), CIC (+), CH50 42	Resolved 10 days after DC MMI	[19]
8	15/F	MMI 10 mg/d for 2 mo	Bilateral lower leg edema	WBC 1460, Hb 6.7, urine protein 100 mg/dL, urine RBC 20-30/HPF with granular cast, ANA 1:640 (+) speckle, anti-dsDNA 43.83 IU/mL, anti-Sm (-), C3 97, C4 14.6, ESR >130/>160 mm, MPO-ANCA (+)	Resolved soon after DC MMI and the lab data returned normal within 40 days	[This study]

Abbreviations: MMI = methimazole; PTU = propylthiouracil; U/A = urinalysis; anti-ENA = anti-extracted nuclear antibody; LE = lupus erythematosus; ANA = anti-nuclear antibody; ESR = erythrocyte sedimentation rate; P-ANCA = perinuclear anti-neutrophil cytoplasmic antibody; CIC = circulating immune complex assay; MPO-ANCA = myeloperoxidase anti-neutrophil cytoplasmic antibody; DC = discontinuation

form mixed disulfides with protein [13]. The main characteristics of LE induced by antithyroid agents are that the mean age was 21.2 years and that there is a female predominance (72.7%) [14].

In the present case, methimazole-induced LE was noted. As for the few other cases that have been reported in the literature with methimazole-induced lupus-like syndrome, they are reviewed in Table 1 [14-18]. Female predominance was noted. The mean age was 16.3 years in females and the only male was 68 years old. The symptoms usually developed between 2 weeks and 4 weeks after medication, but the onset has been reported as long as 4 years after medication as well. The most common symptoms include arthralgia, skin rash and fever, which resolved after discontinuing methimazole. Our case was unique as there was no presentation of arthritis nor skin rash. Instead, she presented with hematological and renal involvement. Her anti-dsDNA antibody was also positive. Although renal involvement and a positive anti-dsDNA are rare in DILE, they are not unheard of and there are still cases reported [9-11]. In this case, the patient's clinical course resolved soon after methimazole was discontinued and after she was put under some steroid and hydroxychloroquine treatment. Since the patient had neither past history nor family history of SLE, we considered this episode to be due to methimazole-induced LE.

In conclusion, we present a rare case of renal involvement and positive anti-dsDNA in methimazole-induced lupus erythematosus in Taiwan. Under the treatment of hydroxychloroquine and levothyroxine, she was free of symptoms after discontinuation of methimazole until now (about 21 months).

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