BRIEF REPORT

METHYLDOPA-INDUCED SYSTEMIC LUPUS ERYTHEMATOSUS

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Thirteen months after starting methyldopa therapy, a 55-year-old white male patient presented with a syndrome of hemolytic anemia, arthritis, photosensitivity, and a positive antinuclear antibody test result. Methyldopa-induced antinuclear antibodies were mainly IgG, directed against class H1 histones. Antibodies to native DNA and nonhistone proteins were not detected. Upon withdrawal of methyldopa therapy, and with a short course of prednisone and danazol therapy, the patient's symptoms and hemolytic anemia resolved. His clinical symptoms and serologic abnormalities returned to normal and remained negative after 2 years of followup.

Several drugs have been implicated in causing a syndrome that meets the criteria for systemic lupus erythematosus (SLE) (1,2). The antihypertensive medication methyldopa has been reported to cause several autoimmune phenomena, including a syndrome that meets some criteria for SLE (3–6). We report a case of well-documented methyldopa-induced SLE, in which the characteristics of autoantibodies produced during the disease course were investigated.

Case report. The patient, a 55-year-old white man, was admitted to Fitzsimons Army Medical Center for evaluation of hemolytic anemia in July 1985. He denied having experienced melena, hematochesia, or other known blood loss, and in January 1985, his hematocrit value had been normal. Thirteen months prior to admission, the patient had been started on a regimen of methyldopa (250 mg twice a day) for control of hypertension. Other medications included dyazide and allopurinol, which he had taken for several years.

Four months prior to admission, the patient had developed arthritis of the hands, wrists, shoulders, knees, and ankles. One month preceding admission, he had developed a photosensitive rash that occurred with as little as 15 minutes of sun exposure. He had experienced increased fatigue, exertional dyspnea, and a weight loss of 5 lb prior to admission, but he denied having any other symptoms.

Results of the physical examination at admission showed normal vital signs. The only abnormalities were swelling and tenderness of the small joints of both hands and wrists, a subconjunctival hemorrhage in the left eye, and minimal nontender splenomegaly. Laboratory investigation showed the following values: hematocrit 26%, hemoglobin 12.6 gm/dl, leukocyte count 7×10^9/liter with a normal differential cell count, platelet count 646×10^9/liter, erythrocyte sedimentation rate (Westergren) 62 mm/hour, reticulocyte count 19.5%, lactate dehydrogenase 500 units/liter (normal <225), and total bilirubin 1.8 μmoles/liter. Findings of other chemistry and coagulation studies and urinalysis were normal. The antinuclear antibody (ANA) test

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Table 1. IgG and IgM antihistone reactivity of serum from a patient with methyldopa-induced systemic lupus erythematosus*

	Histone class						
	H1	H2A	H2B	H3	H4	H2A–H2B complex	Total†
IgG							
At admission	8.2	0.0	0.0	0.0	0.0	0.0	1.1
4 mos. after discharge	0.0	0.0	0.0	0.0	0.1	0.0	0.0
6 mos. after discharge	0.0	0.0	0.0	0.0	0.0	0.0	0.0
17 mos. after discharge	0.0	0.0	0.0	0.0	0.2	0.0	0.0
IgM							
At admission	0.5	0.0	0.1	0.0	0.0	0.0	0.3
4 mos. after discharge	0.7	0.0	0.0	0.0	0.0	0.0	0.5
6 mos. after discharge	0.8	0.0	0.2	0.0	0.0	0.0	0.5
17 mos. after discharge	1.5	0.0	0.7	0.3	0.2	0.0	0.4

* Values are the antibody activity in sera diluted 1:200, as determined by enzyme-linked immunosorbent assay, and are expressed as the mean optical density of triplicate readings at 405 nm. Values >0.3 are significant.
† Total refers to a mixture of all 5 histones.

result was positive at a dilution of ≥1:256, with a homogeneous pattern, on mouse kidney substrate. Rheumatoid factor, lupus erythematosus (LE) cell preparation, and serologic test for syphilis yielded negative results. Serum complement levels, quantitative immunoglobulins, and serum protein electrophoresis findings were normal. The direct Coombs' test result was 4+ positive for IgG and negative for complement; the indirect Coombs' test showed negative results. Findings of a chest roentgenogram and electrocardiogram were normal.

Methyldopa was discontinued, and the patient began taking prednisone (20 mg, 3 times a day) and danazol (200 mg, 4 times a day). His hemolytic anemia and splenomegaly resolved. The prednisone and danazol dosages were tapered over 4 months, then discontinued. He was followed for 2 years and showed no recurrence of previous symptoms.

Methods. Serum samples were drawn from the patient at the time of admission, during the treatment period, and after the prednisone and danazol had been discontinued. Antibodies to nuclear antigens were detected on 4 μm–thick sections of mouse kidney by indirect immunofluorescence. Serum samples were examined for antibodies to native DNA by a Millipore filter (Bedford, MA) binding technique, antibodies to nonhistone antigens (Sm, nuclear RNP, SS-A, and SS-B) by double immunodiffusion, and antibodies to histones by enzyme-linked immunosorbent assay (ELISA), as previously described (7).

Results. Serum samples were collected at admission and 4, 6, and 17 months after the patient's discharge from the hospital. Analysis of each sample showed that the ANA result was positive at admission and negative 4 months after treatment had been started. Likewise, the direct Coombs' test result was 4+ positive at admission and became negative 4 months after initiating prednisone and danazol therapy.

Analysis of the admission serum sample by ELISA showed significant antibody activity to total histones. Other assays showed that the serum did not contain antibodies to double-stranded DNA (dsDNA) or the nonhistone antigens Sm, nuclear RNP, SS-A, or SS-B. After the methyldopa was discontinued, antibody activity to total histones became undetectable in subsequent serum samples.

At the time of admission, antibodies to histones were primarily IgG, directed against the H1 class (Table 1). IgM anti-H1 antibodies in lower titer were also detected. IgG antihistone antibodies became undetectable after the methyldopa was discontinued; however, IgM antihistone antibodies remained detectable at low levels.

Discussion. Definitive criteria for the diagnosis of drug-induced SLE have not been established. The diagnosis is based on the appearance of lupus-like symptoms (2), associated with a positive ANA test result after ingestion of a drug, with resolution of the patient's symptoms and serologic abnormalities after the offending agent has been withdrawn. These criteria were met in the present case, thus showing that methyldopa can cause a lupus-like syndrome.

Although Coombs-positive hemolytic anemia and positive ANA test results are known to occur secondary to methyldopa administration, a review of the literature in the English language show no reports of methyldopa-induced SLE in which 4 criteria for SLE were satisfied. In 1967, Sherman et al described 2

patients, ages 74 and 88, who developed autoimmune hemolytic anemia associated with positive LE cell phenomena, while taking methyldopa (375 mg/day for 17 months and 500 mg/day for 5 months, respectively) (3). In 1971, Eliastam and Holmes described a 40-year-old woman who developed hepatitis, arthritis, and LE cell phenomena after 2 months of methyldopa therapy (750 mg/day) (4). Harrington and Davis described a 50-year-old woman with pleuropericarditis associated with a positive ANA test, who had been taking methyldopa (500 mg/day) for 12 months prior to the onset of symptoms (5). The patient's ANA test result was negative after acid extraction, and pleural fluid complement levels were depressed relative to concomitant serum levels. Finally, in 1982, Dupont and Six described a 48-year-old woman who developed arthralgias, Raynaud's phenomenon, and ANA after taking methyldopa (750 mg/day) for 2 years (6). This patient also had positive LE cell phenomenon and a positive direct Coombs' test result, without evidence of hemolysis. In contrast to these reports, our patient's symptoms (hemolytic anemia, photosensitivity, arthritis, and positive ANA) meet the American Rheumatism Association criteria for SLE (2).

A consistent finding in patients with drug-induced lupus is a positive ANA test result. In patients with procainamide-, hydralazine-, and quinidine-induced lupus, the ANA have been shown to be directed primarily against histone components of the nucleus (8–10). This contrasts with the findings in patients with idiopathic SLE, in whom antibodies against histones, as well as dsDNA and nonhistone proteins, are detected. The ANA profile in our patient is similar to that in other patients with drug-induced SLE, having antihistone specificity without antibodies to DNA and nonhistone proteins. This may be a typical pattern for methyldopa-induced lupus, since the patient described by Harrington and Davis also had ANA that were directed only against histones (5).

The fine specificity of IgG antihistone antibodies in drug-induced SLE tends to depend on the eliciting agent. Most patients with procainamide-induced SLE have autoantibodies against the H2A–H2B complex (11), while patients with hydralazine-induced SLE have autoantibodies that display preferential reactivity with individual histones, H3 and H4 (9). In some patients with procainamide- and hydralazine-induced lupus, sera will also show weak reactivity with H1. Sera from SLE patients react with H1 and several other histones in a nonspecific manner (12). Antihistone antibodies in our patient were directed primarily against H1, without reactivity against other histones.

It is interesting that our patient maintained IgM antihistone antibodies after discontinuing methyldopa therapy. IgM antihistone antibodies do not correlate with systemic disease, in that patients taking procainamide (11) or hydralazine (13) often remain asymptomatic while producing IgM antihistone antibodies. In our patient, the strong antihistone H1 immune response induced by methyldopa may have established IgM anti-H1 antibodies as a permanent part of the B cell repertoire, maintained and driven by endogenously released nuclear antigens. Since discontinuing drug treatment, the patient has remained asymptomatic, with negative Coombs' and negative ANA test results.

Hypotheses explaining the pathogenesis of drug-induced SLE have been reviewed (14) and include cross-reacting autoantibodies between the drug and nuclear proteins, interaction of the drug with nuclear antigens making them immunogenic, and interaction of the drug with lymphocytes (15). Of specific relevance to this case, methyldopa has been shown to inhibit the function of T suppressor cells (16) and may impair reticuloendothelial function that could predispose to a lupus-like syndrome (17). Genetic predisposition and other factors relating to drug metabolism may augment any and all of the above-mentioned theories in the pathogenesis of drug-induced SLE (18).

In summary, we have shown that methyldopa can cause SLE and can induce the production of ANA to a specific class of histone proteins. Methyldopa has also been shown by previous investigators to cause other alterations in the immune system. These mechanisms may be important in generating autoantibodies frequently seen in patients receiving methyldopa, and in causing clinical manifestations of SLE.

REFERENCES

1. Harmon CE, Portanova JP: Drug-induced lupus: clinical and serological studies. Clin Rheum Dis 8:121–135, 1982
2. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, Schaller JG, Talal N, Winchester RJ: The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 25:1271–1277, 1982
3. Sherman JD, Love DE, Harrington JF: Anemia, positive lupus and rheumatoid factors with methyldopa. Arch Intern Med 120:321–326, 1967
4. Eliastam M, Holmes AW: Hepatitis, arthritis and lupus

cell phenomena caused by methyldopa. Am J Dig Dis 16: 1014–1018, 1971
5. Harrington TM, Davis DE: Systemic lupus-like syndrome induced by methyldopa therapy. Chest 79:696–697, 1981
6. Dupont A, Six R: Lupus-like syndrome induced by methyldopa. Br Med J [Clin Res] 285:693–694, 1982
7. Rubin RL: Enzyme-linked immunosorbent assay for anti-DNA and anti-histone antibodies, Manual of Clinical Laboratory Immunology. Edited by NR Rose, H Friedman, JL Fahey. Washington, DC, ASM, 1986
8. Fritzler MJ, Tan EM: Antibodies to histones in drug-induced and idiopathic lupus erythematosus. J Clin Invest 62:560–567, 1978
9. Portanova JP, Rubin RL, Joslin FG, Agnello VD, Tan EM: Reactivity of anti-histone antibodies induced by procainamide and hydralazine. Clin Immunol Immunopathol 25:67–79, 1982
10. West SG, McMahon M, Portanova JP: Quinidine-induced lupus erythematosus. Ann Intern Med 100:840–842, 1984
11. Rubin RL, McNally EM, Nusinow SR, Robinson CA, Tan EM: IgG antibodies to the histone complex H2A-H2B characterize procainamide-induced lupus. Clin Immunol Immunopathol 36:49–59, 1985
12. Craft JE, Radding JA, Harding MW, Bernstein RM, Hardin JA: Autoantigenic histone epitopes: a comparison between procainamide- and hydralazine-induced lupus. Arthritis Rheum 30:689–694, 1987
13. Litwin A, Adams LE, Zimmer H, Foad B, Loggie JHM, Hess EV: Prospective study of immunologic effects of hydralazine in hypertensive patients. Clin Pharmacol Ther 29:447–456, 1981
14. Hess EV, editor: Drug-induced lupus, Proceedings of the Kroc Foundation Conference, Santa Ynez Valley, California, 1981. Arthritis Rheum 24:979–1111, 1981
15. Bluestein HG, Zvaifler NJ, Weisman MH, Shapiro RF: Lymphocyte alteration by procainamide: relation to drug-induced lupus erythematosus syndrome. Lancet II: 816–819, 1979
16. Kirtland HH III, Mohler DN, Horwitz DA: Methyldopa inhibition of suppressor lymphocyte function: a proposed cause of autoimmune hemolytic anemia. N Engl J Med 302:825–832, 1980
17. Kelton JG: Impaired reticuloendothelial function in patients treated with methyldopa. N Engl J Med 313:596–600, 1985
18. Woosley RL, Drayer DE, Reidenberg MM, Nies AS, Carr K, Oates JA: Effect of acetylator phenotype on the rate at which procainamide induces antinuclear antibodies and the lupus syndrome. N Engl J Med 298:1157–1159, 1978