

BRIEF REPORTS

Severe Complication of a Commonly Prescribed Drug: Minocycline-Induced Lupus

John Shepherd, MD

May you never outlive your children.

Native American proverb

The constellation of symptoms that includes persistent fever, weight loss, general malaise with rash, myalgias, and arthritis brings a number of serious conditions into consideration: malignancies, connective tissue diseases, and systemic infections. Drug-induced complications also fall into this differential diagnosis. Drug-induced lupus is most commonly associated with procainamide (first described in 1962), hydralazine, chlorpromazine, isoniazid, α -methyldopa, and quinidine. From 46 to 70 drugs can cause drug-induced lupus, with the first probable case caused by sulfadiazine, published in 1945, and the first definite causal relation with hydralazine described in 1953.¹⁻³ Reports have also implicated the lipid-soluble semisynthetic tetracycline, minocycline, used as a disease-modifying agent for reactive rheumatoid arthritis and for acne.^{1,2,4-14}

In 1959, 3 patients were reported to have developed a systemic lupus erythematosus (SLE-like) syndrome after taking tetracycline.⁴ Since then no other cases of tetracycline-caused drug-induced lupus have appeared. The first case of minocycline-induced lupus was described in 1991.^{4,5,14}

Many adolescents come to their family physicians with concerns relating to acneiform changes in their skin, and 65% of all prescriptions for minocycline are written for acne.⁷ Fifty-seven cases of minocycline-caused systemic lupus have appeared in the medical literature. None, however, has been published in a family medicine journal.⁴ Given the frequency of diagnosis of acne and the common

prescription of minocycline, the possibility of severe adverse reactions from this drug needs recognition.

Case Report

An 18-year-old recent high school graduate looking forward to an enjoyable summer before entering college complained to her physician of fatigue, general malaise, weight loss, fever (to 103°F), rash, sore throat, cervical adenopathy, and joint swelling and arthralgia (primarily ankles). The oldest daughter of 2 physicians, she had an unremarkable medical history other than two knee operations secondary to sports injuries. She had no known recent infectious exposures or travel. She had worked with organic solvents making proteins as a laboratory assistant at a biopharmacology company for approximately 1 month. Her only prescription was for minocycline, which she had been taking for cystic, inflammatory acne for slightly longer than 2 years at a dosage of 50 mg twice a day. She did not take an oral contraceptive.

When examined, she was a thin, slightly pallid girl with shoddy anterior cervical nodes, enlarged red tonsils coated with exudates, and a grade 2/6 systolic murmur heard from the upper left sternal border to the apex. There were no abdominal masses or organomegaly. Her right ankle was edematous, warm, and painful with full range of motion, and there were $\frac{3}{4} \times \frac{1}{2}$ -cm salmon-brown-colored nodular lesions on the anterior and posterior thighs.

Monospot, rheumatoid factor, and tuberculin (PPD) tests were negative, as were throat cultures and two blood cultures. There were normal radiographic findings of the chest and right ankle, and a normal cardiac sonogram. She had a sedimentation rate (ESR) of 12 mm/h, normal electrolyte levels, and normal findings of an urine analysis. Her white cell count was $6.5 \times 10^3/\mu\text{L}$ with a normal differential, normal platelet count, and a normal hemo-

Submitted, revised, 1 December 2001.

From the Department of Family Medicine, School of Medicine, University of Colorado Health Sciences Center, Denver. Address reprint requests to John Shepherd, MD, Department of Family Medicine, PO Box 6508, Mail Stop F496, Aurora CO 80045-0508.

globin concentration. Her liver function tests were elevated with an aspartate aminotransferase (AST) of 536 U/L and alanine aminotransferase (ALT) of 487 U/L, although hepatitis A, B, and C screening tests proved negative. Serologic studies for Epstein-Barr virus noted a positive viral capsular antibody (VCA) immunoglobulin M (IgM) (73 arbitrary units [AU] with <20 AU normal) and positive VCA IgG (170 AU with <20 AU normal); however, no Epstein-Barr nuclear antibodies were found.

One month later with her symptoms and physical examination findings unchanged, her blood tests showed improved liver function tests (AST 139 U/L and ALT 128 U/L), but the hemoglobin level decreased to 12.1 g/dL and ESR increased to 23 mm/h, with C-reactive protein of 12.5 mg/L. Her antinuclear antibody titer was 1:1280 (homogeneous nucleolar), and tests for anti-DNA, ribonucleoprotein, and Smith (Sm) antibodies were negative. An Epstein-Barr nuclear antibody test remained negative.

An appointment was scheduled with a rheumatologist, but before that session the patient's parents read in the *Physician's Desk Reference* about potential lupus-like syndromes from minocycline and stopped the drug. After examining the patient, the consultant ordered a serologic test for perinuclear antineutrophil cytoplasmic antibody and diagnosed infectious mononucleosis and probable drug-induced lupus syndrome.

After her first quarter at college and 6 months after the onset of symptoms, she returned for Christmas break feeling much better and had only the persistent rash. Her laboratory tests showed a hemoglobin level of 14.1 g/dL, an ESR of 7 mm/h, an antinuclear antibody titer of 1:320, and an Epstein-Barr VNA elevated at 20 AU. Her liver function tests had returned to normal.

In August, 1 year later, her antinuclear antibody titer was 1:80.

Discussion

In the United States 500,000 cases of systemic lupus erythematosus purportedly exist, and 10% of them are secondary to medicines.² To diagnose systemic lupus erythematosus, 4 of 11 clinical signs or laboratory findings must be present, whereas drug-induced lupus cannot be claimed unless the person has a positive antinuclear antibody test, one

clinical feature of lupus, and no history of lupus, and the condition improves with the elimination of the offending drug.^{2,3,15} Fifty-seven case reports describe minocycline-induced lupus, one of which included a concomitant infection with Epstein-Barr virus.^{4,12} A substantial number of cases might remain unpublished.¹⁶ Although most drug-induced lupus syndromes resolved, 2 patients died of complications from pancytopenia and hepatic failure.¹⁴ Young women made up the majority of patients (84% with a mean age of 21 ± 8.6 years; range 14–59 years), and all had been taking minocycline for acne.^{4,5,16}

The dosage of the medicine ranged from 50 to 200 mg/d, the median time for taking the drug was 19 months, and the patients had symptoms 1 month to 1.5 years before discontinuing the drug.^{4,5,12} In those whose symptoms resolved after discontinuation, the time to resolution ranged from 2 days to 2 years.^{4,7} All had recurrence of symptoms with drug challenge tests.⁴ All patients also had polyarthritides and arthralgia (usually hands and feet), frequently with fever, malaise, fatigue, and weight loss. Liver disease appeared in 54%, 21% had dermatologic signs, and 14% showed cardiopulmonary abnormalities.^{4,5,7,10,15} One had nephritis. All affected patients had an elevated antinuclear antibody titer (1:20–1:10,000), and 38 of 40 had an increased ESR. The anti-DNA antibody level was high in 15%, and the anti-Sm antibody level was elevated in 41%. The anticardiolipin antibody level was elevated in 33%, perinuclear antineutrophil cytoplasmic antibodies were elevated in 12 of 14 patients, and antihistone antibodies were found in 4 of the 31 patients.^{3,5}

Although some authors have distinguished between autoimmune hepatitis and drug-induced lupus when reviewing the case reports (indeed, hepatitis does not appear on the list of organs involved in systemic lupus erythematosus), others have not separated the two adverse effects because they occur simultaneously and with regularity.^{4,5,10,11,14,15} The concurrent infection with Epstein-Barr virus adds another possible cause for the hepatitis noted in this case.¹⁷

Multiple hypotheses have arisen to explain the mechanism leading to drug-induced lupus: (1) immune response to the drug, metabolite, or a conjugate; (2) interaction of the drug or metabolite with nuclear antigens to increase the immunogenicity of nucleic acids; (3) immunogenetic factors,

such as acetylation phenomena; (4) latent viral infections; (5) human lymphocyte antigen-DR2 immunotype, which is associated with systemic lupus erythematosus; (6) monocytes and neutrophils converting the drug into cytotoxic products; and (7) minocycline metabolites serving as antigens that induce an antibody response cross-reacting with microsomal cytochromes, cytoplasm, and histones.^{2,5-7} None has garnered consistent support, however.^{2,10,12} In addition, different drugs seem to elicit different antibody responses.² The question remains as to how a simple compound of low molecular weight can induce autoimmunity in persons with seemingly normal immune systems.

This case report becomes the 58th documented example of minocycline-induced lupus and the second with concomitant Epstein-Barr infection.^{4,12} The clinical and laboratory data contained in this case correspond closely to the findings described in previously published cases of drug-induced lupus secondary to minocycline. The concomitant Epstein-Barr infection certainly could have influenced the laboratory results, and the combination of diseases might also have worsened the clinical symptoms.^{3,12,17}

Family physicians see adolescents with concerns regarding their complexions for which they often prescribe minocycline therapy. This case description serves as an example of the phenomenon of a common disease treated with a frequently used therapeutic agent leading to an unfamiliar yet severely debilitating and potentially fatal disease. Perhaps the recommendation to monitor liver functions tests and antinuclear antibody status while patients are on minocycline bears some merit.¹⁴ At the very least, primary care providers need to recognize the potential complications of this drug and thoroughly discuss the risks and benefits of its use, while never underestimating the impact of iatrogenic disease on the well-being of patients and their families.

References

1. Crosson J, Stillman MT. Minocycline-related lupus erythematosus with associated liver disease. *J Am Acad Dermatol* 1997;36(5 Pt 2):867-8.
2. Hess E. Drug-related lupus. *N Engl J Med* 1988; 318:1460-2.
3. Rich MW. Drug-induced lupus. The list of culprits grows. *Postgrad Med* 1996;100:299-302, 307-8.
4. Schlienger RG, Bircher AJ, Meier CR. Minocycline-induced lupus. A systematic review. *Dermatology* 2000;200:223-31.
5. Elkayam O, Yaron M, Caspi D. Minocycline-induced autoimmune syndromes: an overview. *Semin Arthritis Rheum* 1999;28:392-7.
6. Elkayam O, Yaron M, Caspi D. Minocycline induced arthritis associated with fever, livedo reticularis, and pANCA. *Ann Rheum Dis* 1996;55:769-71.
7. Akin E, Miller LC, Tucker LB. Minocycline-induced lupus in adolescents. *Pediatrics* 1998;101: 926.
8. Masson C, Chevaillier A, Pascaretti C, Legrand E, Bregeon C, Audran M. Minocycline related lupus. *J Rheumatol* 1996;23:2160-1.
9. Gendi NST, Bowman SJ, Mowat AG. Lupus-like syndrome in patients treated for acne. *Br J Rheumatol* 1995;34:584-5.
10. Angulo JM, Sigal LH, Espinoza LR. Coexistent minocycline-induced systemic lupus erythematosus and autoimmune hepatitis. *Semin Arthritis Rheum* 1998;28:187-92.
11. Knowles SR, Shapiro L, Shear NH. Serious adverse reactions induced by minocycline. Report of 13 patients and review of the literature. *Arch Dermatol* 1996;132:934-9.
12. Farver DK. Minocycline-induced lupus. *Ann Pharmacother* 1997;31:1160-3.
13. Matsuura T, Shimizu Y, Fujimoto H, Miyazaki T, Kano S. Minocycline-related lupus. *Lancet* 1992; 340:1553.
14. Gough A, Chapman S, Wagstaff K, Emery P, Elias E. Minocycline induced autoimmune hepatitis and systemic lupus erythematosus-like syndrome. *BMJ* 1996;312:169-72.
15. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 19-2001. A 50-year-old man with fever and joint pain. *N Engl J Med* 2001;344:1929-35.
16. Singer SJ, Piazza-Hepp TD, Girardi LS, Moledina NR. Lupuslike reaction associated with minocycline. *JAMA* 1997;277:295-6.
17. Rea TD, Russo JE, Katon W, Ashley RI, Buchwald DS. Prospective study of the natural history of infectious mononucleosis caused by Epstein-Barr virus. *J Am Board Fam Pract* 2001;14:234-42.